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## Twentieth Anniversary

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TWENTY years ago this month there appeared the first number of a new publication, the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. It was issued in response to a demand for a successor to follow an honored predecessor, the *American Journal of Obstetrics and Diseases of Women and Children*, which suspended publication, by force of circumstances, in December, 1919, after an uninterrupted career dating back to 1868.

A paragraph from the opening announcement of the new JOURNAL may be quoted in this Preface to the present number, which marks the conclusion of a period of twenty years of similar uninterrupted service to the American medical profession in this field.

"The importance of obstetrics and gynecology as an integral part of medical art and science should be measured not only by its interest to those directly engaged in it as a specialty but likewise to those who practice medicine in a more general sense. A topic that necessarily commands the attention of so many physicians must be adequately represented in journal literature and demands a medium of publication primarily devoted to its advancement and welfare. The present venture has been developed in response to this need."

How successful the venture has been may be measured by the growth of the JOURNAL and its reception by the profession. Among such factors is the increase in the number of specialist societies which have selected the JOURNAL as their official organ and the constantly augmented circle of readers, both here and abroad, to whom the publication appeals as the representative magazine in this field of medical practice in the United States. The demands for space in its pages by authors from all parts of the country constitute a flattering tribute, and so great have these been that all papers emanating from foreign sources have had to be declined for several years. The JOURNAL has retained its catholic character, it has been liberal in its acceptance of contribu-

tions, thus bearing in mind the varying needs of the specialist as well as the general practitioner. The clinician, the pathologist, the research worker, the teacher, and the student have all found a welcome in its pages.

The present issue is intended to be commemorative; it contains a series of brief critical articles by men who have been identified with certain special fields and who have aimed to delineate progress as well as to evaluate the advances which have been made during these past two decades.

The Editors believe that a comprehensive survey of most of the outstanding accomplishments of the period is presented in this anniversary issue. It has not been feasible to include every phase of activity, for the field covered by our specialty has expanded greatly and is no longer limited to the narrower domain characteristic of a half century ago. Gynecology and obstetrics have not only made a closer approach to each other, but they have come to be taught as a unified subject in most of our medical schools and are associated more closely and intimately with the practice of radiology, chemistry, physiology, pathology, and general medicine itself, than was the case in former generations. The increased hospitalization of obstetric patients is likewise a noteworthy development as is the recognition of the need of adequate care for the pregnant woman and of her importance in the social scheme. The strides made in the field of preventive medicine in a larger sense have found likewise their wider application in obstetrics and gynecology. We should be proud to acknowledge the extended participation by American physicians in these advances and their presentation in the pages of the JOURNAL.

To our literary contributors, to our subscribers, to our Advisory Board, to the various societies who have accepted this magazine as their official organ, and to our many friends, the Editors and Publishers of the JOURNAL desire to express their grateful appreciation of the support which has been accorded the venture during these first two decades since its establishment. We trust that we will merit its continuance for many years to come.

George W. Kosmak  
Hugo Ehrenfest  
The C. V. Mosby Company

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We are indebted to Dr. Robert L. Dickinson for the specially designed title page in this issue as well as the photographs of the sculptured models of the "Birth Prelude" and the Stages of Labor. The sculptures were done by Mr. A. Belskie.

## An Appreciation

THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY celebrates with this issue its twenty years of service to the medical profession, a special service, devoted exclusively, as its name implies, to the complementary activities of this important specialty.

It is a great honor to share, even in the smallest way, in this well-earned celebration, to pay a deserved tribute to the coming-of-age, as it were, of this journalistic achievement.

And first, we are mindful that this JOURNAL represents, and so much the better, a second incarnation, inasmuch as it has fallen heir to a rich inheritance of tradition and experience. It has profited thoroughly thereby, for the strength of the old has been utilized to the full in this later and larger existence.

Its distinguished progenitor, the so-called "Blue Journal," was one of our earliest American publications. Founded in 1868, this *Journal of Obstetrics and Diseases of Women and Children*, published by William Wood and Company of New York, enjoyed a long and influential career until it finally succumbed in 1919, as a result of the financial depression of the Great War. Brooks H. Wells, whom so many of us gratefully remember as its Editor-in-Chief, had died in 1917. Very fortunately for the future and for us all, some eight years before his death, he had chosen as his associate editor, George W. Kosmak of New York, and it was upon the shoulders of his enthusiastic associate that the mantle fell. Dr. Kosmak who was to ring out the old, and then to ring in the new, was editor of the *Journal of Obstetrics* for the last two years of its existence and then, after a year's interregnum, the founder and Editor of the JOURNAL that now so ably represents.

This, in a few words, is the history of our JOURNAL, the JOURNAL of our specialty, though nothing is revealed therein of the courage, wisdom, and determination that finally gave it this second birth. We believe that it is fitting to recall something of that famous struggle. Those post-war years were indeed saddened years (this sadness, Heaven knows is with us yet), a time inauspicious for the launching of any enterprise, and especially perhaps for the re-creation of any journal. And yet the Fates were with us, and it was finally accomplished.

It is only fair to say that it was really Dr. Kosmak, a Founder in name and in deed, who drove it through. Loyal friends rallied to his support, notably George Gellhorn of St. Louis, and The C. V. Mosby Company undertook its publication; Hugo Ehrenfest became associate and later co-editor, an advisory board of editors was chosen, as well as a thoroughly representative Publication Committee; and so was born this independent, special JOURNAL, twenty years ago.

And very justly we are proud of it. Even in the adolescent years, it has amply justified its existence, has returned in abundant-fold the terms of its stewardship, and fills today no small place in our medical

literature. Untrammeled by any commercial restraints, it has made and earned its own way, walked upon its own feet, and again we are proud of it.

From the first, it has been particularly fortunate in its Editorial Staff; for while its high ideals have been steadily maintained, the balance has been evenly held as between the laboratory and clinical aspects of the work. In consequence, it adequately meets the requirements of the specialist, the research worker, and the man or the woman in general practice.

Trusted within and without, it has been accepted as the official organ of all our important Societies, and so has become the sponsor, as it were, of their respective transactions. While its pages encouragingly reflect each and every special line of research, there is always manifest a critical censorship, so essential to the integrity of our professional life; so indispensable to the health, welfare, and reputation of our specialty.

We heartily congratulate the JOURNAL, its editors, its publisher, and its staff, and it needs no prophet to foretell a long and brilliant future for this distinguished exponent of the fourth estate.

WALTER W. CHIPMAN.

Montreal, Quebec.

August 14, 1940.

## THE DEVELOPMENT OF THE IMPLANTATION THEORY FOR THE ORIGIN OF PERITONEAL ENDOMETRIOSIS

JOHN A. SAMPSON, M.D., ALBANY, N. Y.

EGHTEEN years have elapsed since the essential features of this theory were published. Ever since that time I have continued to be greatly interested in endometriosis of all types, especially the peritoneal type, not only because it occurs more frequently than all others and is clinically the most important, but also because its pathogenesis is so tantalizingly alluring and elusive.

For over ten years I studied peritoneal endometriosis constantly and intensively, and since then intermittently according to the operative findings in individual cases. During the intensive study of this subject the distribution and character of its lesions were carefully noted at operation. Sketches were frequently made at that time. Great attention was paid to small implants. When feasible these were excised. Drawings, many in color, were made of all specimens of endometriosis before they left the operating room floor. All material was fixed intact in formalin. After fixation, I selected the exact portions of the specimens which I wished to study histologically. This tissue was embedded in celloidin, since it causes less unequal tissue shrinkage than paraffin. I supervised the mounting of the embedded tissue and instructed the technician how it should be cut. A small notebook was carried, in which I jotted down "inspirations" before they vanished. Studies of the peritoneal implantation of cancer cells escaping from carcinoma of the ovary and of the body of the uterus and also studies of the spread of these tumors in other ways, were initiated by my desire to investigate more intelligently the spread of benign Müllerian mucosa.

I enjoyed every bit of the study of endometriosis; there were an abundance of fresh material, excellent laboratory facilities, including well-trained technicians, an artist whose illustrations speak for themselves better than any words I might employ, a cooperative and skilled microphotographer and interested associates. My chief contribution was an insatiable curiosity which, stirred by difficulties and opportunities which were constantly arising, perpetuated my interest.

I greatly appreciate the appraisals of my observations and interpretations which have been made by others. However, it is my own critical evaluation of these observations and interpretations which I shall attempt to present in this review.

The term endometriosis was introduced to indicate the presence of ectopic tissue which possesses the histologic structure and function of the uterine mucosa. It also includes the abnormal conditions which may result not only from the invasion of organs and other structures by this tissue, but also from its reaction to menstruation.

Endometriosis may be divided into two main groups, direct (internal) and indirect (external). In the first the ectopic mucosa, usually situated in either the uterine or tubal walls, is continuous with the mucosa lining these organs. The ectopic mucosa in the second group has the same histologic structure as that in the preceding one but is not continuous with normally situated Müllerian mucosa. If the mucosa in this group is derived from the latter it must arise from the transplantation to and the growth of bits of this tissue in new situations. This phenomenon may be accomplished in various ways.

Peritoneal endometriosis, one variety of the indirect group, is usually found on the surface of the various organs and structures primarily or accidentally situated in the female pelvis, especially those in the posterior cul-de-sac. These foci are nearly always multiple and their distribution is very similar to that of peritoneal carcinomatosis secondary to cancer cells escaping into the peritoneal cavity from carcinoma of the ovary and of the body of the uterus. The majority of the lesions of peritoneal endometriosis are small and superficial. Sometimes, however, this ectopic mucosa invades, much like carcinoma, the organs or structures beneath it. The early deposits of endometriosis on the surface of the ovary often differ in no way from similar deposits in other situations of the same ease. They may remain small and superficial or become invasive and give rise to endometrial cysts of that organ.

Postoperative endometriosis may be either direct or indirect and offers as large and as interesting a field for the study of this subject as experimental endometriosis in the lower animals.

#### THE IMPLANTATION THEORY

Ovarian and other forms of peritoneal endometriosis arise from the implantation of bits of Müllerian mucosa, of either uterine or tubal origin, which, having been carried with menstrual blood escaping through patent tubes into the peritoneal cavity, have lodged on the surfaces of the various pelvic structures. The ectopic mucosa in these implants, regardless of their size or situation, may become additional foci for the spread of the endometriosis by direct extension and also by the implantation of bits of Müllerian tissue which escape from them during their reaction to menstruation. This latter phenomenon is most spectacular in the ovary where ectopic endometrial cavities may attain a much larger size than elsewhere, forming the well-known endometrial cysts of that organ.

#### OBSERVATIONS AND INTERPRETATIONS MADE DURING THE FIRST STEP IN THE DEVELOPMENT OF THE IMPLANTATION THEORY

In the year 1921 I reported 23 cases of endometrial cysts of the ovary under the title "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary: Their Importance and Especially Their Relation to Pelvic Adenomas of Endometrial Type ('Adenomyoma' of the Uterus, Rectovaginal Septum, Sigmoid, etc.)."

Since the study of the material obtained from this group of cases furnished not only the first step in the development of the implantation theory but also both the incentive for and the key to its completion, I am republishing the following verbatim excerpts from the conclusions of the original paper.

"At operation the cyst or ovary is found to be adherent, and in freeing it the 'chocolate' contents escape because a previous perforation, which had been sealed by whatever structure the ovary had become adherent to, is reopened or the cyst is torn. Adhesions, due to the irritating action of the material which had previously escaped from the ovary, are always present, and these vary greatly in location, density and extent. They may be found in any of the natural pockets and folds of the pelvis where such material would be apt to lodge, and especially in the cul-de-sac."

"The exact counterpart of the epithelial lining of these ovarian hematomas may be found in the uterine hematomas often occurring in adenomyoma of the uterus and apparently due to the retention of menstrual blood. Tissue of endometrial type is also present in pockets in the periphery of the ovary about the perforation, and the tissue in these pockets may resemble normal endometrium more closely than that lining the hematoma in the same ovary. The histologic study of these hematomas shows that periodic hemorrhage, similar to that of menstruation, occurs. I have come to the conclusion that these ovarian hematomas are of endometrial type just as are the uterine hematomas found in adenomyoma of the uterus."

"The adhesions form equally as interesting a pathologic study as the cysts themselves because adenoma of endometrial type is present in the tissues involved by the adhesions in a large percentage of cases. I have studied histologically the tissues involved by the adhesions outside of the ovary in fourteen of the twenty-three specimens, and adenoma of endometrial type was found in thirteen of these."

"Sometimes, or possibly many times, in the life of these hematomas, material including epithelial tissue and blood (menstrual) may escape into the peritoneal cavity from the hemorrhagic cyst or from the endometrial pockets in the ovary about the site of perforation and lodging in the natural pockets and peritoneal folds of the pelvis, they may cause adhesions. Adenomas of endometrial type often develop between the adherent folds of peritoneum thus resulting. These adenomas may be small and quiescent or they may be invasive. *If invasive they may cause adenomyoma of the uterus by invasion of the uterine wall from without or adenomyoma of the uterosacral ligament, round ligament, rectovaginal septum, rectum, sigmoid, etc., namely, whatever structure or organ is invaded by the adenoma arising from the infective contents of the cyst or ovary lodging on its surface.* The question naturally arises: In what way do the contents of the cyst or ovary cause the development of these adenomas? Is it due to some specific irritant present in the cyst contents which stimulates the peritoneal endothelium, thus causing a metaplasia and the development of endometrial tissue typical both in

structure and in function? Some may assert that dormant endometrial epithelium may be present in the tissues soiled by the contents of the cyst and this is stimulated to further growth. *It seems to me that the condition found in many of these specimens is analogous to the implantation of ovarian papilloma or cancer on the peritoneal surface of the pelvis from the rupture of an ovarian tumor containing these growths.*"

A critical evaluation, based on further studies and greater knowledge, of the observations and interpretations recorded in the first paper follows. The validity of all of the observations has been confirmed by subsequent studies. However, some of the interpretations are not entirely correct.

I then believed that these cysts arose either from a metaplasia of the surface epithelium of the ovary or from congenitally misplaced epithelium of endometrial type in that organ. These theories are not as convincing to me, at the present time, as the implantation theory.

The conclusion that menstruation occurs in these cysts and produces hematomas of endometrial type, identical with those found in adenomyoma of the uterus, has been strengthened by further observations.

The assumption that the fusion of an ovary containing one of these cysts with an adjacent structure is always an indication of the sealing of a perforation of the cyst is not correct. From subsequent studies of the development of endometrial cysts of the ovary I have learned that they arise from Müllerian tissue on the surface of that organ (nearly always the lateral or under surface). Frequently there also is endometriosis on the posterior surface of the uterus or broad ligament in contact with the infected surface of the ovary. These surfaces frequently become adherent to each other before the ovarian cyst actually develops. This fusion arises from two sources: first, the irritation of the peritoneum and surface of the ovary by menstrual blood escaping from the endometriosis in these situations, and second, by the frequent continuity of the ectopic mucosa on the surface of the ovary and adjacent structures. The cyst subsequently developing in the ovary may be entirely surrounded by ovarian tissue, but often a portion of its wall is formed by the uterus or parietal peritoneum fused with the ovary in this situation, thus presenting the appearance of a sealed perforation of the cyst.

The inference that endometrial cysts actually rupture and their contents escape into the pelvic cavity has been confirmed by finding this phenomenon at operation. When pressure is made on such a cyst at that time, more of its contents escape through an opening in its wall at or near its fusion with an adjacent structure. If these patients had not been operated upon, the perforation would later have become sealed and the cyst might again rupture at a later menstrual period.

Subsequent studies of the conditions present in patients with evidence of a recent rupture confirm the original interpretation that the material escaping from these cysts may be very irritating to the peritoneum and adhesions may arise from it, both locally about the site of rupture and also in other portions of the pelvis, especially the bottom of the posterior cul-de-sac. Adenomas of endometrial type (endometriosis) were found in a large percentage of the pelvic structures apparently

soiled by the contents of these cysts in the first series of cases studied. Subsequent studies have confirmed this observation. At the time the first paper was published I believed that the Müllerian mucosa in the above described situations arose from the implantation, on the surface of the peritoneum, of epithelium cast off by the menstrual reaction of the lining of the ovarian cyst and carried with its contents, escaping into the pelvic cavity. I also believed that a similar phenomenon occurred from the menstrual reaction of endometrial mucosa on the surface of the ovary about the site of the fusion of the cyst with adjacent structures. Strong circumstantial evidence indicates that peritoneal endometriosis arises from ovarian endometriosis in this manner. Proof will be presented showing that it also arises from other sources and that at least in certain instances some peritoneal endometriosis was present in the pelvis prior to the rupture of the ovarian cyst.

The first step in the development of the implantation theory consisted of strong circumstantial evidence, indicating that peritoneal endometriosis could arise from the implantation of epithelium carried with menstrual blood escaping into the peritoneal cavity from foci of endometriosis in the ovary.

A CRITICAL EVALUATION OF THE OBSERVATIONS AND THE INTERPRETATIONS  
MADE DURING THE SECOND STEP IN THE DEVELOPMENT OF  
THE IMPLANTATION THEORY

This was reached in 1922, the year following the publication of the first paper. As a result of greater ability in recognizing the lesions of peritoneal endometriosis at operation, 33 cases of this condition associated with endometrial cysts of the ovary were encountered in one year, as compared with 23 similar cases which had been previously collected over a period of more than ten years. During the same period, 15 additional cases were studied in which there was no gross evidence of an endometrial cyst in either ovary. One or both ovaries had been removed in 13 cases. In 9 of these, tubules or glands of Müllerian type were found on either the lateral or under surface of the ovaries. These were interpreted as structures from which endometrial cysts might arise. In 4 cases no evidence of ovarian endometriosis was detected. Subsequent studies have resulted in similar observations and interpretations.

It was noted that the early lesions of endometriosis on the surface of the ovary and peritoneum in some cases not only had the same gross appearance and histologic structure but also appeared to be of the same age. Similar observations have repeatedly been made since then. Therefore a common source for the endometriosis in both situations was sought. Naturally patent tubes were considered as possible avenues through which Müllerian tissue might escape into the peritoneal cavity.

In the 56 cases of endometrial cysts of the ovary which had been studied up to that time the tubes appeared normal and patent in all. In the 15 cases of peritoneal endometriosis without demonstrable endometrial cysts of the ovary, the tubes appeared normal and patent in all but one. In that case bilateral hematosalpinx was present without evi-

dence of endometriosis in either ovary. The histologic structure of portions of the mucosa of the occluded fimbriated ends of the tubes in this case was similar to that of the mucosa in the associated implant on the posterior surface of the uterus. Bearing in mind the manner of the spread of endometriosis from the ovary to the peritoneum, I inferred that this implant might have arisen from tubal epithelium cast off by the menstrual reaction of the tubal mucosa prior to the complete occlusion of the tubes. I believe that this inference is correct.

Material escaping through patent tubes, therefore, was considered as a possible cause of both ovarian and other forms of peritoneal endometriosis. My present reactions in regard to the above observations and interpretations of the same are well expressed in a paper published in 1927. A verbatim excerpt from this paper follows. "One of the outstanding features of patients with peritoneal endometriosis is that the tubes are usually patent. In 293 cases of peritoneal lesions containing endometrium-like tissue encountered during the last five years, both tubes appeared to be patent in 284, a unilateral hematosalpinx in 3 (in 2 of these blood was present in the opposite tube but the tube was patent), bilateral hematosalpinx in 4, and bilateral pyosalpinx in 2. Patent tubes apparently increase the incidence of peritoneal endometriosis and possibly the relatively large number of patients with hematosalpinx (7) may be of some significance. In the 6 cases with occlusion of both tubes, the peritoneal lesions might have been present prior to the closure of the fimbriated ends of the tubes. It would seem that during the menstrual life of women some substance escapes from the tubes into the pelvis which plays an important role in the etiology of pelvic peritoneal endometriosis, including the development of endometrial tissue in the ovaries. This substance may be menstrual blood in some instances and tubal secretion in others. In either case epithelium may be present."

From careful anatomic studies of the relation between the fimbriae of normal tubes and the surfaces of the ovary and other structures in the pelvis, which were made at that time, I inferred that if implants should arise from epithelium escaping from the mucosa of the tube including its fimbriae or from the uterus, they would occur most frequently on the lateral and under surfaces of the ovaries, the lower portions of the posterior surfaces of the uterus and broad ligament and in the bottom of the cul-de-sac. It is in these situations that the early implants of peritoneal endometriosis had been most frequently observed. Similar observations have been made in subsequent studies.

The variations in the type of the epithelium (either uterine or tubal) in peritoneal endometriosis, the occurrence of mucosa in the fimbriae and ampulla of the tube having the structure and function of the endometrium, and the incidence of direct endosalpingosis of endometrial type following salpingectomy and tubal sterilization, all suggest that peritoneal endometriosis could be derived from tubal as well as from uterine mucosa.

The peritoneal endometriosis associated with endometrial cysts of the ovary, which I had studied up to and including 1922, was more

extensive and invasive than that occurring without these cysts. For these reasons the ovary was considered an incubator, hotbed, or even at times an intermediary host in the development of implants on the peritoneum, and might even impart greater virulence to the Müllerian epithelium growing in it. The larger cysts were accompanied by greater pelvic adhesions and a more extensive peritoneal endometriosis than that accompanying the smaller cysts. The study of more material has taught me that extensive peritoneal endometriosis occasionally occurs without any demonstrable ovarian endometriosis and large and very adherent endometrial cysts with extensive adhesions in the cul-de-sac are encountered in which very little endometriosis is found in the organs and other pelvic structures involved by these adhesions. Therefore the suggestion that the ovary may impart greater virulence to the Müllerian epithelium growing on it is unwarranted.

It is true that there is *no positive proof* that epithelium escaping from these cysts becomes implanted on the peritoneum. However, a careful study at operation of the conditions present in a large number of cases of endometrial cysts will convince even the most skeptical observer that the material escaping from these cysts frequently causes adhesions, and the evidence indicating that the Müllerian mucosa in these situations at times comes from the contents of the cyst is very strong.

Because I believed in 1922 (and still believe) that implantations on the peritoneum arise from epithelium carried by menstrual blood escaping from ovarian endometriosis both from the cysts and the non-encapsulated endometrium on the surface of the ovary and also from endometrial foci in the tubal mucosa, I suggested that menstruation with a backflow through the tubes may play an important role in the etiology of ovarian and other forms of peritoneal endometriosis. At that time I did not know whether or not this phenomenon occurred.

Since 1922 many patients, requiring pelvic operations, have purposely been operated upon during menstruation. Not infrequently blood was observed escaping through the patent abdominal ostia of the tubes of these patients. This occurs in patients with and without peritoneal endometriosis. Bits of viable appearing uterine mucosa surrounded by blood were found in sections of some of the above described tubes after they had been fixed in formalin.

The detection of peritoneal endometriosis with and without ovarian involvement led to the second step in the development of the implantation theory. This consisted of strong circumstantial evidence indicating that bits of Müllerian tissue, derived from both the uterine and the tubal mucosa and carried by menstrual blood escaping through patent tubes into the peritoneal cavity, could become implanted on various pelvic structures including the ovaries, and the resulting perforating hemorrhagic ovarian cysts are only spectacular foei in the secondary spread of endometriosis.

Subsequent studies have shown that a secondary spread of endometriosis also could arise from foci in other situations than the ovary. This latter phenomenon constituted the third and final step in the development of the implantation theory.

## SUMMARY

In studying the pathogenesis of ovarian and other forms of peritoneal endometriosis, one must not lose sight of the important role evidently played by patency of the tubes.

At times, during menstruation, blood, carrying bits of Müllerian mucosa, escapes through patent tubes into the peritoneal cavity. This blood may come either from the uterine or from the tubal mucosa. Circumstantial evidence indicates that Müllerian tissue in this blood, under favorable conditions, becomes implanted on any structure upon which it may lodge. These early primary implants occur most frequently in close proximity to the distal ends of the tubes, such as the lateral and under surfaces of the ovary, the lower portions of the posterior surfaces of the uterus and broad ligaments, and the bottom of the cul-de-sac. They may be present only on the ovary or ovaries, only on the peritoneum, or in both situations. Some of these implants remain small and superficial. The Müllerian mucosa in others invades its host much like implantation carcinoma. When it invades other organs or structures than the ovary, a type of endometriosis arises which both grossly and histologically often closely resembles a direct endometriosis of the uterine wall.

The invasion of the ovary by Müllerian mucosa implanted on its surface and the conditions resulting from it are in many ways similar to those arising from the invasion of the other organs and structures by this tissue except for one very striking difference. The ectopic endometrial cavities distended with menstrual blood in endometriosis, in other situations than the ovary, are usually small while those in the ovary frequently attain a large size, forming the well-known endometrial cysts of that organ. Whether small or large these ovarian cysts often rupture and some of their contents escapes into the peritoneal cavity frequently causing adhesions, and, under favorable conditions, the judged peritoneal implantation of bits of the epithelial lining of the cyst which had been cast off by menstruation. In patients with peritoneal endometriosis associated with an endometrial cyst of the ovary, both primary implants from or through the tubes and secondary ones from the cyst may be present.

The study of peritoneal endometriosis also indicates that menstrual blood may not only escape from foci of endometriosis in other situations than the ovary, but adhesions and an additional spread of the endometriosis (secondary implants) may arise from this source. On account of the usual small size of the superficial foci of serosal endometriosis, the results of their participation in menstruation are not as striking as those which take place in the ovarian cysts.

If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive.

The viability of this theory is of secondary importance to me as compared with the pleasure and the increased knowledge of this and kindred subjects which I have gained in these studies and the resulting more intelligent treatment of patients who have peritoneal endometriosis. There are many other interesting unsolved problems associated with the pathogenesis and life history of endometriosis of all types. Since it is my desire to adhere strictly to the text which has been assigned me, I have not discussed any of these.

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## THE MORE RECENT CONCEPTIONS OF THE PELVIC ARCHITECTURE

W. E. CALDWELL, M.D., F.A.C.S., H. C. MOLOY, M.D., M.Sc., AND D. ANTHONY D'ESOPO, M.D., NEW YORK, N. Y.

RECENT anatomic and roentgenologic studies have shown, to the satisfaction of most observers, that variations in the size and shape of the pelvis occur more frequently than was hitherto suspected. Certain characteristic types have been described in detail and more recent studies have gone far toward appraising the significance of these variations upon the mechanism of labor. The chief differences in opinion among interested workers, at the present time, concern the correct classification of these variations. The material that follows will be limited to the more important observations we have made during the last eight years in a study directed toward the description and classification of these variations.

### CLASSIFICATION OF PELVES

In studying the classifications proposed by such authorities as Michaelis, Litzmann, Tarnier, Budin, Schauta, Breus and Kolisko, and others, some wholeheartedly accepted the principle that an obstetric classification should be arranged according to the etiology of the factors which caused the distortion. They attempted to fit abnormalities of doubtful origin into appropriate sub-groups. Others, recognizing the prevalence of pelvic abnormalities for which no known explanation existed, introduced such morphologic terms as "flat nonraehitic pelvis," "funnel pelvis," or "generally contracted type." Although Michaelis and Litzmann favored the morphologic school of thought, the preconceived methods of etiologic grouping and lack of concrete knowledge prevented the general acceptance of their views. Anatomists and anthropologists have always considered form in the study of unknown skeletal material. Stein (1825) distinguished four groups: (1) Elliptical with the greatest diameter anteroposterior, (2) round, (3) elliptical with the greatest diameter transverse, (4) blunt-heart shaped. Turner in 1885 proposed a morphologic classification based upon the relationship between the transverse and anteroposterior diameter of the inlet. He divided pelvis into three groups: (1) Dolichopellic, in which the conjugate vera is greater than the transverse, (2) mesatipellic, in which the conjugate vera and transverse diameter are of equal length, (3) platypellic, in which the conjugate vera is shorter than the transverse diameter. Thoms has recently revised Turner's classification and has added a fourth group, the brachypellic form. During the early part of this century, anthropologists made a number of significant observations which have not been fully appreciated. Wood Jones and Elliot Smith, during excavation in Nubia in 1906, observed numerous examples of extreme masculine types of female pelvis. Derry, Straus,

and others, have described in detail the masculine characteristics which may aid in the determination of the sex of unknown skeletal material. Recent anthropologists such as Hrdlička, Todd, Hooton, Schultze, Shapiro, and others, are convinced that the variations in pelvis are too complex to be grouped in the simplified classifications proposed by Weber, Stein, and Turner. Shapiro, at the American Museum of Natural History, has summarized anthropologic opinion by considering these diversified forms as *normal growth variants*.

This brief review of the literature gives the requirements which must be fulfilled by any comprehensive classification. A classification of pelvis which will prove of maximum clinical value and lead to a better understanding of the mechanism of labor is based, necessarily, on morphology. It should be comprehensive enough to permit the classification of rare forms as well as the common types. It should provide an accurate description of the pelvic canal as well as the inlet and outlet. A suitable terminology, with appropriate descriptive terms, must be devised to enable obstetricians to give a reasonably accurate concept of the size and shape of the pelvis as a whole. We have attempted to fulfill these requirements in the classification described in this report.

Eight years ago at the Sloane Hospital for Women a group became interested in the causes of dystocia. In a short time, from the study of skeletal pelvis at the American Museum of Natural History, New York; the United States National Museum, Washington; and especially Todd's large collection of pelvis of known sex at Western Reserve University, Cleveland; and by roentgenologic examinations upon living women, we recognized the types described by Stein and Turner and the masculine form long known to anthropologists. The reports of Wood Jones, Berry Hart, Derry, Straus, and others, were most helpful in the analysis of these variations. We found that division of the inlet into an anterior and posterior segment at the widest transverse diameter aids in the analysis of pelvic shape. The posterior segment behind the widest transverse diameter is formed by the sacrum and a portion of the two iliae bones above the sacrosciatic notch. The anterior segment in front of the widest transverse diameter is formed by a small portion of both iliae bones and the superior rami of the pubis along the iliopectineal lines.

The study of this material resulted in the recognition of four parent, or pure, types to form the basis for a morphologic classification of pelvis. The following terms were proposed to describe the parent types:

#### PARENT TYPES

1. *The Anthropoid Type* (Greek, *Anthropos*, human being + *Eidos*, resemblance). This pelvis resembles the shape of the pelvis of the anthropoid apes. The anterior and posterior segments together present a long narrow oval shape. The side walls are straight, the subpubic arch is under average in size, and in the classic type, the sacrum shows an average inclination.

2. *The Gynecoid Type* (Greek, *Gynē*, woman). This is the so-called normal female pelvis. The anterior and posterior segments give a round or transverse slightly ovoid shape. The side walls are straight, the subpubic arch is wide, and the sacrum shows an average to backward inclination.

3. *The Platypelloid Type* (Greek, Platys, flat, + pellis, pelvis). The anterior and posterior segments combine to give a transverse oval or flat form. The side walls are straight and the subpubic arch is wide.

4. *The Android Type* (Greek, Aner, man). This type bears a resemblance to the male pelvis at the inlet and at lower levels. The posterior segment is flat and the widest transverse diameter is close to the sacrum. The anterior segment is triangular in shape. The two segments combine to produce a wedge-shaped appearance. At lower levels, the side walls show convergence, the subpubic arch is narrow, and the sacrum is forward.

Each pure type shows a characteristic shape for both segments at the inlet and also at the mid and lower pelvis. Pure types occur less frequently than "mixed" forms which reveal a departure from the characteristic shape of the parent type either at the inlet, in the pelvic cavity, or in both. Certain pure types with characteristic inlet shapes may show variations below the inlet. These forms are classified according to the inlet shape, augmented by descriptive terms which describe the lower pelvic deviations. For instance, pelvis which reveal anthropoid or gynecoid inlet types become "mixed forms" through the presence of convergence of the side walls, a narrow subpubic arch, a forward lower sacrum, or some other departure from the classic anthropoid or gynecoid pure type. Android types may become "mixed forms" by revealing straight side walls, or a wide subpubic arch, or any other departure from the classic android shape in the mid or lower pelvis.

In other mixed types, the inlet differs from the pure forms in addition to the presence of lower pelvic variations. These forms require a modified terminology to define the inlet shape before the lower pelvis is described. In these examples the posterior segment may conform to the shape of one parent type and the anterior segment to that of another. In the classification of these mixed types, the first term indicates the shape of the posterior segment, and the second term the shape of the anterior segment. Theoretically at least, the posterior segment of any one of the four parent types may be combined with the anterior segment of the other three to give three mixed forms. For example, the gynecoid posterior pelvis, when associated with the anterior segment of an anthropoid, android, or flat parent type, results in "gynecoid-anthropoid," "gynecoid-android," and "gynecoid-flat" types.

The anthropoid posterior segment combines commonly with only *two* parent anterior segments, the gynecoid and android, to form "anthropoid-gynecoid" and "anthropoid-android" types. Theoretically at least, an "anthropoid-android" type could occur to designate anthropoid types with a narrow fore pelvis, but these forms are usually considered as pure anthropoid types. At the present time, our knowledge of these variations is too incomplete to assume that a narrow fore pelvis necessarily represents a masculine characteristic in all instances. For example, the term "gynecoid-android type," described above as a gynecoid mixed type, actually refers to a "gynecoid pelvis with a narrow fore pelvis." We have encountered a few examples in which the shape of this narrow fore pelvis appears to resemble a masculine characteristic, but in others, the narrow fore pelvis does not present a

masculine appearance. It may resemble the type of narrow fore pelvis commonly found in anthropoid forms.

The combination of an anthropoid posterior pelvis with a flat anterior segment is, of course, impossible.

The android posterior segment is frequently found associated with a gynecoid, anthropoid, or flat anterior segment to produce "android-gynecoid," "android-anthropoid," and "android-flat" forms. We have suggested that the term "android," when used as the second term in mixed forms, indicates a narrow fore pelvis. "Android-anthropoid" types likewise possess a narrow fore pelvis. The anthropoid character, indicated by the second term, is caused by the long anterior sagittal diameter. The posterior segment of flat types likewise may be associated with gynecoid or android anterior segments to produce "flat-gynecoid" and "flat-android" mixed types. These mixed flat types are difficult to distinguish from "gynecoid-flat" and "android-flat" forms. Although we have included "flat-gynecoid" and "flat-android" types in the formal classification, in actual practice, mixed flat forms are classified usually as the "gynecoid-flat" or "android-flat" variety.

Following the classification of the inlet shape, the variations in the mid and lower pelvis must be considered before a comprehensive classification has been obtained. In spite of a desire for simplicity, the occurrence of lower pelvic deviations necessitates the use of further descriptive terms. Fortunately, for many years, obstetricians have used terms such as "wide" or "narrow" subpubic arch, "prominent ischial spines," or a "forward lower sacrum." For practical purposes, we have found that the list of terms, given elsewhere in this report, adequately describe the pelvis below the inlet, in the classification of routine case studies (see classification Group II). The comprehensive description and classification of variations in the pelvis, as outlined above, was incorporated into a work sheet which we used in charting the frequency of occurrence of the various types. This work sheet, as originally devised, included fourteen parent and mixed types along with appropriate descriptive terms for the mid and lower pelvis (see complete classification).

In reporting the observations gained from the use of this work sheet in the study of routine cases, we departed from the original fourteen types. We did not include the "anthropoid-android" and the "gynecoid-android" types, because we failed to apply rigidly the principle that the term "android," when used as the second term in a mixed type, indicates a narrow fore pelvis. As a result, the gynecoid-android type was classified as a "gynecoid or normal pelvis with a narrow fore pelvis." Many anthropoid types with a narrow fore pelvis were classified as pure types. A few of these forms are, however, more correctly considered as "anthropoid-android" types. In the original article we described three flat forms: the "gynecoid-flat," the "android-flat," and the "true flat" or platypelloid type. If, however, careful attention is directed to the study of the shape of the anterior and posterior segments in flat forms, "flat-gynecoid" and "flat-android" types may occasionally be found.

Dr. Kyle B. Steele, at the New York Lying-In Hospital, during the last few years, has made extensive use of our original work sheet. He has recognized the fourteen inlet types and has devised standard shapes (in cardboard) for the anterior and posterior segments of the four parent forms. These inlet tracings may be fitted into the image in the precision stereoscope to aid in the diagnosis of unusual mixed forms. They are excellent for teaching purposes. In his opinion, the principle of combining anterior and posterior segments represents a comprehensive and practical method for the recognition of the pure and mixed forms. Other workers, among them Rappaport and Seadron, Pettit and associates, and Walsh, have reported similar observations.

We have studied, up to the present time, over 3,000 roentgenologic case studies; in not more than an estimated 2 per cent has a recognized cause for the pelvic abnormality been found. Rickets accounts for about half of these, or 1 per cent of all pelvises studied, and the other half is accounted for by a variety of causes. Many of these distinctly pathologic types may retain their primary shape to such a degree that the pelvis may be classified upon a morphologic basis similar to the classification of the normal growth types. The degree of the pathologic distortion can be described in general terms. If approximately 98 per cent of all pelvises are considered normal growth variants, it follows that the classification of these forms must be placed on a morphologic basis and given prominence in all formal classifications.

Hitherto, we have made no attempt to combine these morphologic forms with the infrequent pathologic types in a classification. Recently this was done through the interest of Dr. Henricus Stander. All the rare forms described in the last edition of Williams' textbook have been included. The complete classification as approved by Dr. Stander is arranged as follows:

#### MORPHOLOGIC TYPES

##### I. Normal Female Growth Types:

(Each inlet type must be augmented with appropriate terms to describe the lower pelvis chosen from list of terms given in Group II.)

|                             |   |
|-----------------------------|---|
| 1. True anthropoid type     | Transversely contracted type                |
| 2. Anthropoid-gynecoid type | Anthropoid with narrow fore pelvis          |
| 3. Anthropoid-android type  | Normal female pelvis                        |
| 4. True gynecoid type       | Gynecoid with narrow fore pelvis            |
| 5. Gynecoid-anthropoid type |   |
| 6. Gynecoid-android type    | Masculine type, funnel type                 |
| 7. Gynecoid-flat type       |   |
| 8. True android type        |   |
| 9. Android-anthropoid type  |   |
| 10. Android-gynecoid type   |   |
| 11. Android-flat type       |   |
| 12. True platypelloid type  |   |
| 13. Flat-gynecoid type      | Difficult to distinguish from gynecoid-flat |
| 14. Flat-android type       | Difficult to distinguish from android-flat  |

##### II. Terms Used in Describing the Morphology of the Mid and Lower Pelvis to Augment the Inlet Classification:

|  |                       |
|--|-----------------------|
| 1. Pelvic size                                   | Large, average, small |
| 2. Pelvimetry measurements of cardinal diameters |                       |

|                                |  |
|--------------------------------|--|
| 3. Posterior segment of inlet  | Gynecoid, android, anthropoid, flat  |
| 4. Anterior segment of inlet   | Wide, average, narrow  |
| 5. Symmetry of inlet           | Symmetrical, asymmetry to right, asymmetry to left   |
| 6. Pelvic bones                | Heavy, average, light  |
| 7. Retropubic angle            | Wide, moderate, narrow   |
| 8. Subpubic arch               | Wide, moderate, narrow   |
| 9. Pubic rami                  | Straight (Gothic arch) or curved (Norman arch)   |
| 10. Pubic symphysis            | Masculine or feminine type   |
| 11. Side walls of pelvis       | Divergent, straight, or convergent   |
| 12. Ischial spines             | Long, sharp, or flat   |
| 13. Apex of sacrosciatic notch | Wide, average, narrow  |
| 14. Base of sacrosciatic notch | Wide, average, narrow  |
| 15. Sacrum                     | A general concept of length, width, number of segments                                       |
| 16. Sacral curvature           | Straight, average, marked  |
| 17. Sacral inclination         | (a) upper portion—forward, average, backward<br>(b) lower portion—forward, average, backward |
| 18. Shape of terminal sacrum   | Blunt, average, sharp  |
| 19. Lateral bore               | Straight, convergent, divergent  |

#### PATHOLOGIC TYPES

##### III. *Abnormal Growth and Developmental Types:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Infantile
2. Dwarf

##### IV. *Types Caused by Disease of the Pelvic Bones and Joints:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

###### A. Metabolic:

1. Rachitic:
  - a. Flat
  - b. Generally contracted and flat
  - c. Generally contracted
2. Osteomalacia

###### B. Congenital, infectious, and atypical types:

1. Assimilation pelvis
2. Split pelvis
3. Naegele's pelvis
4. Robert's pelvis
5. Coxalgia
6. Coxarthrolisthetic
7. Pelvis spinosa
8. Neoplastic

###### C. Traumatic types:

1. Fracture of pelvis
2. Separation of symphysis

##### V. *Types Secondary to Abnormalities in the Spinal Column:*

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Kyphotic pelvis
2. Kyphorachitic pelvis
3. Scoliotic pelvis
4. Kyphoscoliotic pelvis
5. Kyphoscoliorachitic pelvis
6. Spondylolisthetic pelvis

**VI. Types Secondary to Abnormalities of the Lower Extremities:**

(In addition to the abnormality the pelvis may be classified morphologically as outlined in Groups I and II.)

1. Luxation of femora
2. Atrophy or loss of one or both extremities

In the study of routine cases, "mixed" types may occur which afford great difficulty in their correct grouping within this morphologic classification. A certain pelvis, to one observer, may conform to the "gynecoid-anthropoid" type, while to another it may resemble the "anthropoid-gynecoid" form. Hrdlička has intimated that many pelvises may be encountered which are difficult to classify, inasmuch as one normal growth type blends imperceptibly with another. Pelvises which tend to favor one or more of the mixed types usually possess compensatory space due to the well-formed anterior or posterior segment. This latter point should be emphasized in the description of these unusual mixed forms rather than the precise inlet classification. In most instances the pelvic inlet is symmetrical but minor examples of asymmetry may occur. A few of these asymmetrical types may show masculine characteristics on one side, while the other displays the usual female contours.

Since a simple morphologic classification of a few standard types is totally inadequate, the obstetrician must finally accept the fact that the best classification is one which enables him to appreciate the obstetric capacity of the pelvis, and to use descriptive terms which convey a reasonably accurate concept of the pelvis as a whole. From the standpoint of roentgenologic technique, these variations in pelvic morphology cannot be studied with accuracy by single flat anteroposterior films. Stereoroentgenograms viewed in the precision stereoscope which corrects distortion should form the basis for the roentgenologic technique if accuracy in the classification of the pelvis is desired.

**CLINICAL RECOGNITION OF THE ABNORMAL PELVIS**

Pelvises with ample diameters and a wide subpubic arch may be classified as gynecoid types. On x-ray examination, these cases may prove to be ample anthropoid types, or even large android forms. When the promontory can be reached, the diagnosis of a flat type is made, if the pelvis seems wide at the interspinous diameter. If, however, the ischial spines are prominent, the sacrosciatic ligament is short, the saerum is forward, and the subpubic arch is narrow, the diagnosis of a true android type may be made. The small gynecoid type may be difficult to recognize, because it suggests one of the more abnormal forms. But this is not a serious clinical error, since a small gynecoid type may give rise to as much dystocia as other abnormal forms.

Extreme anthropoid types are quite easily recognized clinically. The diagonal conjugate is long, and the promontory cannot be reached, except in the small types. The diagnosis is dependent upon the recognition of a decrease in transverse space throughout the pelvis, not only at the interspinous level, but in the regions above the ischial spines. In

anthropoid types, the sacrospinous ligament is long if the sacrum has an average inclination. The narrow retropubic angle can also be palpated.

In the typical android type, the sacrosciatic notch is narrow, the sacrum has a forward inclination, and the sacrospinous ligament is short. It is important to distinguish between the adequate pelvis with a forward lower sacrum and android types in which a forward sacrum represents only one of the many masculine characteristics present.

Occasionally the recognition of a narrow subpubic arch leads to the diagnosis of an android or anthropoid type. Although a narrow subpubic arch is more commonly associated with these primary types, certain gynecoid forms may also demonstrate this abnormality in the lower pelvis. We advise an x-ray examination for all cases clinically suspected of possessing one or more abnormalities. Study of the stereorontgenograms either confirms the obstetrician's clinical impression or indicates the source of his error.

#### ROENTGENOLOGIC RECOGNITION

Certain roentgen methods of pelvimetry have been simplified to consist of not more than two films, a lateral and an anteroposterior view. While these views are adequate for the purpose of roentgen measurement, they are not satisfactory for a comprehensive study of pelvic morphology.

Our interest in the morphology of the pelvis in living women led Dr. Golden and Dr. Swenson, of the Roentgen-Ray Department of Presbyterian Hospital, to suggest the use of stereorontgenograms. This method has been found entirely satisfactory for visualization of the pelvis and the fetal pelvic relationship. The technique includes stereorontgenograms, a lateral view and a forty-five-degree angle view of the subpubic arch. One of us (H. C. M.) has developed a stereoscope which allows the observer to measure the phantom image, and to obtain dimensions of the cardinal pelvic diameters.

While exact diameters may be attained by roentgen methods, in actual practice the significance of these measurements is difficult to determine. One of the serious drawbacks to the use of a few cardinal diameters as a basis for prognosis is the fact that compensatory space does not enter into such calculations. We are opposed to the use of roentgen methods of prognosis which are based on the results obtained from mathematical formulations of a few pelvic and fetal diameters. The ultimate outcome of labor depends upon many other factors. The intricate variations in pelvic shape, although theoretically expressable in centimeters, cannot be so designated in practice; they can only be observed and expressed in descriptive terminology.

## CHANGING CONCEPTIONS OF OVARIAN TUMORS

HOWARD C. TAYLOR, JR., M.D., NEW YORK, N. Y.

THE last twenty years have witnessed unexpected progress in the study of the nature and behavior of ovarian tumors. The greatest advances have, surprisingly enough, been made in those aspects which had previously been regarded as more or less complete, namely in the basic problems of morphology and classification. Clinical advances for the most part have occurred secondarily as the result of a better differentiation of the individual types of ovarian new growth and in a clearer grasp of the special manifestations of each.

In 1920 the most commonly accepted classification of ovarian tumors differed little from that of Pfannenstiel,<sup>40</sup> published before the turn of the century. Yet observations were already in the literature which would later force a reclassification, and in 1920 there were signs that a change was imminent. Norris<sup>30</sup> in the first volume of this JOURNAL described an "ovary containing endometrium" and recalled a similar case reported by Russell<sup>45</sup> in 1899. At this time Sampson's<sup>46</sup> first paper, showing the extraordinary frequency of the endometrial new growths of the ovary, must already have been in preparation. As an introduction to another group of neoplasms, von Kahlden<sup>14</sup> in 1895 had reported what appears to have been a granulosa-cell tumor under the title "graafian follicle adenoma" and twenty years later Meyer<sup>23</sup> had described both the cylindromatous and folliculoid types. American gynecologists were, however, to remain completely unaware of these new growths for some years thereafter and to continue to refer vaguely to the "solid tumors of the ovary." The Brenner tumors, which had probably first been noted by Orthmann<sup>39</sup> in 1899 and described anew but erroneously classed as "oophoroma folliculare" by Brenner<sup>3</sup> in 1908, were to wait still longer until 1932 for their status to be clarified (Meyer<sup>27</sup>). Piek<sup>41</sup> had reported the testicular adenoma in 1905, but again many years were to pass before any special attention was to be accorded the arrhenoblastoma (Meyer<sup>25</sup>). Dysgerminomas, finally, were in 1920 a confused group, lost under a variety of titles. Instead of these tumors, more or less familiar to present-day gynecologists, there flourished a variety of now apparently extinct forms, large-cell carcinomas, endotheliomas, embryonal carcinomas, round cell sarcomas, peritheliomas, and a list of growths supposed to be of teratoid origin.

### REORGANIZATION OF THE PATHOLOGY OF OVARIAN TUMORS

The work of the last twenty years, headed by a few outstanding contributions, has been participated in by pathologists and gynecologists throughout the world. These by their combined efforts have sorted out the newly recognized varieties of ovarian tumor and are now gradually accumulating the material to show their frequency, special clinical char-

acteristics and particularly their relative malignancy. To evaluate this work, it is necessary to consider the progress made with each type of neoplasm.

*I. Cysts of the Follicle and Corpus Luteum.*—That the simple cysts based on persistent follicles or corpora lutea were not true tumors has long been recognized. Newer conceptions have served to emphasize this distinction and to place the cystic Graafian follicle or corpus luteum among the signs of disturbed ovarian function and to remove them more definitely from the list of ovarian neoplasms. Their fuller understanding has become a problem for the endocrinologist.

*II. Endometrial (Chocolate) Cysts.*—The years since the publication of Sampson's<sup>46</sup> paper have been much occupied with controversy as to the source of the abnormally placed tissue. Its origin has been claimed to lie in viable fragments of uterine mucosa, passing through the tubes at the time of menstruation (Sampson<sup>46</sup>); in particles transplanted by way of the lymphatics (Halban<sup>13</sup>; Mestitz<sup>22</sup>); in a metaplasia of the serosa at the site of the new growth (Meyer<sup>24</sup>; Lauche<sup>18</sup>; Novak<sup>32</sup>), and in the epithelium of degenerating follicles or corpora lutea (King<sup>15</sup>). The controversy, though undecided, has added a store of incidental information about the disease which has aided in establishing the clinical picture and formulating a general plan of reasonable therapy. Nevertheless, since the origin of the disease is not agreed upon and may even lie outside of the ovary itself, the endometrial cysts must be given a special position as distinct from all of the definitely primary ovarian tumors.

*III. The Primary Tumors of the Ovary.*—Views now generally held apparently require that there continue to be three groups of primary ovarian tumors that have been accepted, and a fourth whose discovery is essentially the work of the last twenty years. To these may perhaps be added for convenience a fifth group to include miscellaneous or rare tumors whose very existence is somewhat in doubt.

*A. The Epithelial Tumors:* These must be divided, of course, into two distinct types, the one based on a "serous," the other on a "pseudomucinous" epithelium. These two have been recognized for many years and little has recently been accomplished towards determining their cause or the source of the cells composing them.

In one respect, however, some advance has been made with these, namely in the better evaluation of the histologic criteria of their malignancy. Twenty years ago many reports betrayed an unprecise use of the term "cystadenoma," for a percentage of such tumors were evidently regarded as malignant and caused recurrences, as did the papillary cystadenocarcinomas. Although the terms are now used more consistently, the extraordinary difference in the rate of cures still reported for cancer of the ovary by different observers strongly suggests that successful statistics are the result of the inclusion in a given series of at least a certain number of essentially benign tumors.

The Brenner tumor, a newly recognized form, is perhaps best classifiable with this group. The presence in the tumor of mucous glands and its not infrequent concrecence with a pseudomucinous cyst (Abraham<sup>1</sup>;

Kleine<sup>17</sup>) suggest its close relationship. Its rare and relatively slight clinical significance seems to forbid an independent position in any classification. Some anglicized version of the name suggested by Plaut,<sup>43</sup> "fibroepithelioma mucinosum benignum," would appear a logical designation. The Brenner tumor probably bears the same relationship to the pseudomucinous cystadenoma as that of another solid tumor, the rare "fibroma adenocysticum serosum" (Frank<sup>19</sup>; Neumann<sup>29</sup>) to the serous cystadenoma. A vast simplification would follow the adoption of the terms, pseudomucinous fibroadenoma (Brenner) and serous fibro-adenoma (Frank).

The Brenner tumor, although first reported in Germany, has been much studied in this country. Among the earliest reports were two cases published in this JOURNAL in 1934 (Wolfe and Kaminester<sup>37</sup>; Maury and Schmeisser<sup>20</sup>). The present knowledge of this tumor has been well summed up by Novak and Jones<sup>37</sup> who noted that up to 1938 one hundred and twenty-two cases had been reported in the literature. These tumors are almost invariably benign and exert no endocrine influence. The principal problem they present is the confusion that they may cause the uninformed who often mistake them for granulosa cell tumors, endotheliomas or even Krukenberg tumors.

**B. The Connective Tissue Tumors:** The benign fibroma of the ovary has, in general, maintained its classic position among ovarian tumors, although a few of the growths formerly placed in this division have recently had their classification altered to that of theca cell tumor.

The once not unusual sarcoma of the ovary has on the other hand all but disappeared. One group, until recently called large round cell sarcoma, has been re-examined and its members distributed among the granulosa cell tumors and the disgerminomas, while more and more of the so-called fibrosarcomas have been conceded to be benign and regarded as simply cellular fibromas. Taylor and Masson<sup>4</sup> noted four instances of fibrosarcoma arising among 280 specimens of fibroma, and even of these none had developed metastasis or recurrence when their paper was published. For contrast it is interesting to note that Scheffey<sup>47</sup> in 1925 had found reports which indicated that sarcoma represented about 4 per cent of all ovarian tumors. The question now may be asked whether there has ever been a sarcoma of the ovary unless the granulosa cell tumor be accepted as arising from the stroma cells and therefore essentially a malignant connective tissue tumor.

**C. Teratomas:** The status of the common cystic teratoma or dermoid has not changed in the last twenty years, and few determined efforts have been made to solve the perplexing problem of its origin. Reports have continued to indicate that not too infrequently dermoids may give rise to squamous cancer (Counsellor and Wellbrock<sup>6</sup>). A type of teratoma, the struma ovarii, has received some special attention and the functional behavior of its thyroid tissue studied (Plaut<sup>44</sup>). Malignant teratomas have been occasionally reported, but it now appears that they too have lost some of their representatives to other classifications.

**D. Specific Tumors of the Ovary:** For several years it has been common practice to associate three ovarian tumors together, namely the

granulosa cell tumor, the arrhenoblastoma, and the dysgerminoma. There is some justification for this grouping, since the origin of each, according to current theory (Meyer<sup>26</sup>), is to be found in the specific gonadal cells and with each there is a relationship to the hormones of the gonad or to the development of the secondary sex characteristics. These qualities and the symptoms dependent upon them are too familiar for repetition here, but certain points in the development of the knowledge of these tumors deserve comment.

1. *The granulosa cell tumors.* The apparent importance of the granulosa cell tumors has steadily increased, as their frequency has become more evident. On account of its suggestive structure the folliculoid type was the first to attract attention, but recognition of various less definite forms having a cylindromatous, acinar, or even diffuse structure soon followed. To this basic group must now, tentatively at least, be assigned two somewhat more distinct forms, the "luteinized" granulosa cell tumor or "folliculoma lipidique" of Lècene (Moulonguet<sup>28</sup>) and the theca cell tumor. Some controversy exists over the possible identity of the "luteoma" and the "hypernephroma" of the ovary, although examples of granulosa cell tumors with isolated areas of luteinization appear to establish the occurrence of at least the partially luteinized form (Plate<sup>42</sup>; Traut and Butterworth<sup>54</sup>; Traut, Kuder and Cadden<sup>55</sup>). The existence of the theca cell tumor also can scarcely be questioned (Löffler and Priesel<sup>19</sup>; Melnick and Kanter<sup>21</sup>), but a disagreement exists as to whether it should be placed in the granulosa cell group or given an independent status. A difference in age incidence, in cellular morphology, and in lipid distribution suggests that they be segregated as a special type (Geist<sup>11</sup>) but their probable common origin from ovarian mesenchyme, their common property of hormone production and the occurrence of an occasional tumor combining both theca and granulosa cell elements seem to permit their classification as a subdivision of the granulosa cell group.

As a result of these accretions the granulosa cell tumors have become not infrequent. By 1936 Novak and Brawner<sup>34</sup> were reporting that 14 per cent of a series of 300 malignant ovarian neoplasms were of this type. Klaften<sup>16</sup> noted a frequency of 10.1 per cent of 188, and Föderl<sup>8</sup> 18 per cent of 319 primary ovarian cancers.

The degree of malignancy of the granulosa cell tumors has not been finally settled. In general they are probably less liable to lead to a fatal recurrence than are the common papillary cystadenocarcinomas. However, to call a tumor benign simply because there is no recurrence after its removal is a fallacious line of thought, though it appears to have been followed by some writers. Varangot,<sup>56</sup> after reviewing reports of 261 cases of granulosa cell tumor, noted that in 10 per cent metastases were already present at the time of the operation and that, particularly if the patients were followed for a long period of time, late recurrences were common. The histologic criteria of malignancy in these cases are badly in need of study.

The origin of the granulosa cell tumors also has been a matter for dispute. The older theories derived them from various sources, from

the celomic endothelium, from the granulosa cells of the follicle, or from embryonal rests of these cells ("granulosaballen"). The extraordinary work of Furth and Butterworth<sup>10</sup> on the production of granulosa cell tumors by the irradiation of the ovaries of mice contains evidence that these tumors may arise on the basis of regenerative processes in the remnants of follicular epithelium or in the interfollicular spindle-shaped cells themselves. This origin from the ovarian mesenchyme has also been favored by Traut and Butterworth.<sup>54</sup> Such a view is rather shattering to the conventional theory of origin of the active cells of the ovary from the germinal endothelium but is supported by Fischel's<sup>7</sup> evidence for the origin of the follicular epithelium from the ovarian mesenchyme.

2. *The arrhenoblastoma* has made itself known on account of the bizarre masculine changes which take place in the female constitution when such a tumor is growing. The tumor is of course not of great practical importance, for Novak<sup>33</sup> could find but 45 reported cases in the literature up to 1938. Its scientific importance lies in the information it contributes to the origin of certain of the secondary sex characteristics. This whole relationship has, however, remained greatly confused by the appearance of signs of virilism with what appear to be hypernephromas of the ovary (Novak<sup>33</sup>), as well as in cases of apparently typical granulosa cell tumors (Bergstrand<sup>2</sup>).

3. *The dysgerminoma*, the third of the three special tumors, is of interest because of its morphologic identity with a tumor of the testis and because of its tendency to occur in pseudohermaphrodites. This tumor also is probably more frequent than was once supposed. Klaften<sup>16</sup> notes that dysgerminomas represented 3.1 per cent, and Föderl<sup>8</sup> 4 per cent of all malignant ovarian tumors.

The question of the malignancy of this tumor is likewise still being studied. Seegar<sup>53</sup> has reviewed 98 cases and found that about 50 per cent of the patients have remained well for five years. Föderl,<sup>8</sup> however, noted that among 55 cases reported in the literature and followed over an adequate period of time, 68 per cent had developed metastases. These figures certainly establish the malignancy of most of these tumors, and it seems questionable whether benign forms of dysgerminoma exist.

*E. Tumors of Doubtful Status:* Besides the list of currently acceptable ovarian tumors, there have always been a few others. These are either somewhat discredited forms still prized by the more traditional pathologist or newcomers, candidates vigorously supported by their discoverers. Most of them are sufficiently rare to make it necessary for judgment on them to be long delayed. Of the first group may be mentioned the endothelioma or perithelioma which is perhaps on its way to the discard. Of the second group is the mesonephroma, described recently by Schiller<sup>50</sup> but still waiting to attain recognition. Finally there is the hypernephroma which for years has contended with the luteoma for a position among the ovarian tumors (Schiller<sup>49</sup>; Glynn<sup>12</sup>; Novak<sup>33</sup>; Novak and Wallis<sup>38</sup>).

## A PROVISIONAL CLASSIFICATION OF OVARIAN TUMORS FOR 1940

Before outlining the classification which the work of the last twenty years appears to have led to, several principles which should govern any modern classification may be suggested.

1. Although it has been said for years that a classification based on histogenesis is not possible, most classifications have attempted to segregate groups which are histogenetically similar although the actual histogenesis may not be known. This principle should be continued.
2. The ancient division into cystic and solid tumors should finally be abandoned, since these gross characteristics have neither important diagnostic nor prognostic significance.
3. That practically all varieties of ovarian neoplasm have benign and malignant counterparts is now pretty evident, and this may well become an assumed vertical division of all true tumors of the ovary. This will make unnecessary the formal repetition of the entire list under both benign and malignant headings.
4. A prerequisite for any acceptable classification of ovarian tumors is that it represents as nearly as possible the general opinion of the time and not simply the private views of some individual theorist.

## A CLASSIFICATION OF OVARIAN TUMORS

- I. Dysfunctional cysts of the follicle and corpus luteum.
- II. Endometrial cysts and endometriosis.
- III. Primary neoplasms of the ovary.
  - A. Epithelial tumors.
    1. Serous cystadenoma and cystadenocarcinoma.  
Special type: Adenoid cystic fibroma (Frankl).
    2. Pseudomucinous cystadenoma and cystadenocarcinoma.  
Special type: Mucous fibroepithelioma (Brenner).
  - B. Connective tissue tumors.
    1. Fibroma and fibrosarcoma.
    2. Rare connective tissue tumors (Myoma, lymphangioma, etc.)
  - C. Teratomas.
    1. Dermoid (cystic teratoma).
    2. Complex (solid) teratoma.  
Special type: struma ovarii.
  - D. Tumors arising from the specific cells of the gonad.
    1. Granulosa cell tumor.  
Special types: a. Folliculome lipidique (Lecene)  
b. Theca cell tumor.
    2. Arrhenoblastoma.  
Special type: Testicular adenoma (Piek)
    3. Dysgerminoma.
  - E. Doubtful tumors.
    1. Endothelioma.
    2. Hypernephroma.
    3. Mesonephroma (Schiller).
- IV. Metastatic tumors of the ovary.

## THE CLINICAL ADVANCES OF TWENTY YEARS

Only one-tenth of this review remains to be devoted to the advances in the clinical field. This is not an unreasonable proportion, however, for the main features of diagnosis and treatment of ovarian tumors have

changed little in the last two decades. In particular in only a few respects have advances been made which were not incidental to the basic changes in pathologic conceptions just outlined.

*Symptomatology.*—The chief contribution to the symptomatology of ovarian tumors has been made in respect to the special tumors and the changes in the secondary sex characteristics dependent upon the hormones produced by them. Besides this really important advance, there may be mentioned only a commoner recognition of the acute symptoms associated with a ruptured follicle cyst and perhaps a better understanding of the effects of ovarian tumors complicating pregnancy and labor.

*Treatment.*—Progress in the treatment of ovarian tumors was to be looked for chiefly in the field of the malignant growths. The surgery of ovarian cancer has, however, altered little, if at all, and the beneficial effects of radiation have remained more a promise than an actuality. Improvement in the results of treatment has perhaps occurred, but inconsistencies in classification, differences of opinion on the histologic criteria of malignancy, and defects in follow-up organization have made statistics alleged to prove this point all but valueless.

Before considering the claims made for radiation therapy, it should first be noted that without it the cure rates as reported have varied from 9.5 per cent (Schleyer<sup>51</sup>) to 53.8 per cent (Norris and Murphy<sup>31</sup>). On account of this discrepancy in basic figures, no statistics using a five-year standard of cure are able conclusively to demonstrate the advantages of radiation. Nevertheless, isolated observations of the shrinkage of palpable tumors, following x-ray therapy and experiences with apparently hopeless cases in which the patients have recovered and lived well beyond the five-year period, indicate beyond doubt that in some instances at least radiation is an effective agent in treatment. Progress in this direction can only be made by meticulous histologic classification and its careful correlation with the effect of therapy. This is perhaps the direction that the advance of the next twenty years will take.

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## CERTAIN OUTSTANDING TRENDS IN GYNECOLOGY DURING THE PAST FORTY YEARS

ROBERT T. FRANK, M.D., NEW YORK, N. Y.

MY PERSONAL experience goes back forty years. In 1900, although gynecology was already a very active specialty, many technical developments were still in their infancy. For example, in that year, the question of whether the cervical stump remaining after supravaginal hysterectomy for fibroids should be buried, the uterine arteries separately ligated, or the cervical stump drained through the lower end of the abdominal incision was still in active debate, as shown by presentations and discussions taking place at the meetings of various specialist societies. Such well-known figures as Howard A. Kelly, Davenport, and E. Lapthorn Smith of Canada took part in this, and yet, Emil Ries of Chicago, Wertheim of Vienna and a few others, had successfully performed radical abdominal removal for carcinoma of the cervix several years previously.

During this same period, violent discussions were frequent as to whether acute salpingitis should be operated upon in the "hot stage" or allowed to go to the interval before operative intervention was undertaken. At operation it was also debated whether these patients should be drained abdominally. A number of lives were needlessly sacrificed by the less conservative surgeons who, without selection, routinely performed operations on acute pus tubes or even acute salpingitis.

The treatment of cystocele, rectocele, and prolapse was likewise in a very unsatisfactory state. Particularly the older group of operators was satisfied to resect the anterior and posterior mucosa for cystocele and rectocele and suture the superficial defects they had created, without regard for the underlying fascial and muscular structures. Prolapse was almost universally treated by ventrofixation in addition to vaginal plastic, although some operators utilized the round ligaments with the hope of giving additional support by placing the uterus in anteflexion. The results with rectocele were much better than with cystocele. It was still the custom to perform multiple operations such as nephropexy with appendectomy (through the same incision), anterior and posterior colporrhaphy and ventrofixation at the same session on patients suffering from enterotaxis.

Although the technique of transabdominal operation was in the formative stage, many operators, in fact more than today, had developed great skill in the vaginal approach. This was due to the fact that until improvements in aseptic technique had rendered transabdominal section less dangerous, the mortality by the vaginal route was far smaller. Vaginal hysterectomy including removal of large fibroids by morcellation was frequently resorted to. Ovarian cysts and inflamed adnexa, as well as ectopic gestations, were successfully removed from below.

In passing, I should mention that the question as to whether a ruptured ectopic pregnancy should be operated upon in the tragic stage was as yet an open one. This was largely due to our inability to restore exsanguinated patients by means of blood transfusion, the sole available remedies consisting of intravenous normal saline solution, exaggerated Trendelenburg position, bandaging of the extremities, and sedation for shock.

The treatment for sterility and dysmenorrhea was on the whole purely mechanical. Opening of the cervical canal by the Pozzi procedure and straightening of the canal by means of the Dudley operation were the rage. No means of recognizing tubal obstruction were available except by opening the abdomen. The stem pessary was freely employed for the relief of dysmenorrhea, sometimes followed by severe pelvic infections. A few pioneers experimented with Fliess's method of cauterizing the nasal mucosa to relieve dysmenorrhea.

In the same year, 1900, A. W. Johnstone, apparently unchallenged, spoke as follows at a meeting of the American Gynecological Society: "There is not one iota of proof that the ovary has any other function than the manufacture of eggs." Eleven years later, such authorities as J. M. Baldy and J. Monro Kerr, still voiced somewhat similar sentiments.

In the second decade of the twentieth century, a great change in viewpoint is noted. Purely mechanistic concepts were in part replaced by greater reliance on a foundation of pathology. A number of voices were raised modestly in the wilderness in favor of a more physiologic point of view. This evidently was sensed by Dr. Robert L. Dickinson when he delivered his presidential address before the American Gynecological Society in 1920. He referred to the gynecologist as follows: "Surgery we have promoted. But if we be just surgeons, by surgeons we may be displaced." The gynecologist need not blush for the advances that he has inaugurated before and since 1920; these advances are of the utmost importance in every branch of medicine.

In the intervening twenty years between 1900 and 1920, technical procedures were standardized. The well-trained gynecologist the world over performed supravaginal hysterectomy for fibroids, radical hysterectomy for carcinoma of the cervix, removal of ovarian neoplasm, salpingectomy or salpingo-oophorectomy for ectopic gestation, as well as other intra-abdominal operations in almost identical fashion. There remained few if any who still advised operation for adnexal diseases in the acute stage.

During the search for improvement in the relief of cystocele, rectocele, and prolapse, intensive study of pelvic anatomy had progressed. Two schools of thought resulted: The one relied mainly on muscular support (the levators and the perineal muscles); the other concluded that the fascial and connective tissue strands (base of the parametria, pubocervical tissues) gave the main support. In consequence of these anatomic researches, the operations practiced for prolapse included sutures of the levator plates, shortening of the parametria, vaginal

hysterectomy, interposition of the uterus, and various abdominal or vaginal fixations. The use of the Manchester operation was still limited mainly to the English school.

In the interim, the gynecologic armamentarium as well as that of the rest of the profession had been greatly enriched by many new discoveries. I mention only a few: The Wassermann reaction enabled us to diagnose syphilis even in its latent stages. Blood transfusion, both by the direct and indirect method, robbed ruptured tubal pregnancy of much of its dangers. The discovery and the use of x-ray and of radium proved a boon in the treatment of menorrhagia, of certain uterine fibroids, and of carcinoma of the cervix. A real renaissance of physiotherapy developed, applicable in gynecology to the treatment of chronic adnexal diseases. Endocrinology, which later on was to grow and spread with the rapidity of a weed, was still a modest bud just poking its head above ground and yet attracting the interest of those in search of the new and promising. Over-optimists were already recording wonder cures with "endoerine products," since proved to be inert and now relegated to oblivion.

World-wide movements for promoting and popularizing the practice of contraception, antenatal care, recognition of early cancer were developing and helped to educate the laity. With all due modesty, we may state that the gynecologist continued to stay in the van of progress, fully utilizing the nova available.

A survey of the present must lack perspective and, therefore, proves difficult, and in the light of tomorrow, perhaps misleading.

The trend during this last decade, at least for the intellectually honest and best informed, is largely away from operative measures. This applies, for example, to the treatment of carcinoma of the cervix in which radiation therapy by means of x-ray and radium has displaced surgery except in the hands of a few. Carcinoma of the corpus uteri, however, is still treated mainly by hysterectomy. In the treatments of fibroids of the uterus, the indications between the choice of operation or radiotherapy have become clear-cut and well defined, based largely upon the findings during preliminary exploratory curettage.

A great improvement has taken place in the early cure of gonorrhreal diseases and some of the more newly classified venereal infections such as lymphogranuloma and granuloma venereum. Complete cure of gonorrhea in its earliest stages, before it has reached the tubes and peritoneum, can be obtained by hyperthermia. By means of chemotherapy with sulfanilamide and its congeners, not only gonorrhreal but also streptococcal infection has been arrested and cured in both the early and later stages of the disease. In consequence, the well-trained gynecologist limits operation to chronic recurrent adnexal inflammations.

For the cure of prolapse, the English Manchester (Donald, or misnamed Fothergill) operation has made major strides in the United States and promises to displace other techniques in the near future.

Mechanical (tubal) sterility can now be recognized or excluded by means of Rubin's insufflation test, and the location of atresias or stric-

tures determined by uterosalpingography with harmless water-soluble and readily absorbed radio-opaque media.

The preoperative diagnosis of functionally active ovarian tumors is now feasible based on their clinical symptoms or the biologic changes they produce. These growths include arrhenoblastoma, granulosa, and theca cell tumors, all of the ovary, as well as chorioneopthelioma, wherever it may originate or metastasize.

Endocrinology has become an important discipline of medical science. In the development of this branch of medicine, gynecologists have taken a prominent part. It is now accepted that functional diseases of the female may originate not only in the ovary but also in the pituitary, adrenal, or thyroid glands. Our point of view concerning the significance, importance, and treatment of functional amenorrhea, bleeding, sterility, and dysmenorrhea has been entirely revised, but doubtless will undergo much further revision before stabilization is arrived at. In bleeding, for example, the uterine mucosa is regarded merely as a labile and changeable indicator of ovarian and other endocrine activity. Much advance can be recorded in the recognition of underlying causes which produce these functional disturbances.

Treatment is in a most chaotic stage; this, in spite of the fact that pure crystalline estrogens, progestational products, and androgens are now available, supplemented by a host of similarly acting synthetic products. The gonadotropic substances remain in an impure state and are as yet of little practical value. Striking results in the treatment of the menopause have been obtained. The huge and cumbersome literature, particularly that of purely clinical nature, which has been accumulating rapidly, will doubtless eventually be forgotten.

The advances of the last twenty years have been aided by a tendency toward accuracy and control, as shown by reliance on investigative machinery, by the employment of rigid statistical methods, by the development, with the aid of physiologists and biochemists, of standardization of bio-assay and chemical assays. The employment of primates, particularly the higher monkeys, in some researches, has made application of the results obtained more readily transferable to the human being.

What advances the future has in store, I would not venture to predict. That gynecology and the other branches of medicine steadily will progress seems assured.

## AN EVALUATION OF THE TREATMENT OF UTERINE CANCER

WILLIAM P. HEALY, M.D., NEW YORK, N. Y.

**I**N REVIEWING the developments in the field of uterine cancer in recent years, they would seem to fall in two major groups: one dealing with diagnosis, the other with treatment.

Cullen in 1909 in the preface to his splendid work on *Cancer of the Uterus* said: "The number of cases of cancer of the genital tract coming too late for operation is so appalling that the surgeon is ever seeking to devise ways and means by which the dread malady may be more generally detected at the earliest possible moment—at a time when complete removal of the malignant tissue is still possible."

Only in recent years, one might say since the establishment of the American Society for Cancer Control, has any well-organized and continued effort been made to reach the lay public and to impress it with the character of such symptoms as may indicate the presence of cancer and the urgent need of prompt medical examination in order that the disease may be detected if present. Despite opposition to these publicity campaigns from within and without the medical profession, largely based on the assumption that much "cancerphobia" would be established and little good accomplished, the work has gone on and the American Society for Cancer Control now is acknowledged as a vital force of great value in its chosen field.

As a result of this publicity a large part of the public has become cancer conscious, and it has been comparatively easy to educate its members to the value of periodic medical examinations at intervals of a year or less.

Equally as important to the patient and the gynecologist has been the need of educating the medical practitioner in the essentials of a thorough investigation of the patient's symptoms, including, when possible, inspection, palpation, instrumentation and last but not least removal of a portion of any suspected lesion for microscopic study.

One would be rash indeed to state that either the public or the medical profession is fully alive to its responsibilities in this regard. Nevertheless one is inclined to believe that "early diagnosis," the first of the essentials in a proper approach to the cure of a patient with uterine cancer, is now better understood and more quickly and logically sought, especially by the general practitioner.

In an effort to help solve the cancer problem, several institutions dealing exclusively with cancer have been established in this country and, equally as significant, so-called "tumor groups" made up of a small cross section of the visiting staff have been formed in many hospitals to further the study of cancer.

Moreover recently the federal government has entered the field, established an Advisory Cancer Council, and funds have been as-

signed for clinical and research fellowships. All this indicates an awakening of a substantial and constructive nature to the requirements of the problem and is most encouraging.

The almost utter hopelessness of the surgical prognosis in cancer of the uterine cervix at the opening of the present century may be judged by Cullen's statistics of patients under observation and treatment at the Johns Hopkins Hospital from 1893 to 1899 inclusive. He reports a total of 141 patients, in 73 of whom the disease was regarded as operable, and an attempt at surgical cure was made. Four of these patients survived five or more years, a cure rate of 5.5 per cent. In the remaining 68, only curettage was done, and the duration of life thereafter must have been brief. Thus there was in this series of 141 cases of cancer of the cervix a total five-year salvage by surgical methods of 1.6 per cent.

In 1900 and 1901 Wertheim published his papers describing a radical type of abdominal hysterectomy for the operable cases of cervical uterine cancer. These papers created at the time a great deal of discussion and were more or less enthusiastically received. A most important feature of his operation lay in a wide excision of the parametrium. Wertheim also emphasized the frequency of involvement of the pelvic lymph nodes by metastatic cancer as he found them in about one-third of his operable cases. It soon became evident that the radical abdominal hysterectomy of Wertheim extended the field of operability in cancer of the cervix. In its essential features it consisted of a wide excision of the parametria, a low amputation of the vagina and removal of the pelvic lymph nodes. In the removal of the parametria, the ureters were laid bare, and often either accidentally injured or their circulation interfered with so that necrosis and leakage subsequently occurred.

Wertheim's percentage of three-year cures and later on, five-year cures, obtained by his procedure were so much better than any previously obtained by surgical methods that there was prompt recognition of the merits of the procedure, and it was widely taken up by gynecologists.

From the first it was realized that great surgical skill was required to perform properly the operation. Gynecologists soon discovered that there were not enough operable cases to permit more than a few of them to develop a satisfactory surgical technique. The mortality associated with the operation was unduly high. Wertheim was said to have had a 30 per cent mortality in his first 100 operations, and Bonney, a more modern and highly efficient technician, reports a 20 per cent mortality in his first 100 cases. The question soon arose as to whether removal of the pelvic lymphatics held out much additional hope of permanent cure.

Wertheim in his early reports stated that the disease had recurred in all cases in which he found the lymph nodes involved at the time of operation, therefore he regarded their removal as of prognostic value only.

Bonney reports that the regional lymph nodes were carcinomatous in 42 per cent of his operable cases, and he states that about one in five of such cases survived five years and that the operative risk in these cases was 20 per cent as against only 10 per cent where there was no regional lymph gland involvement.

Bonney's paper read before the American Gynecological Society in 1935, in which he gave a critical review of his experience with the Wertheim operation covering a period of twenty-eight years from 1907 to 1935, may be regarded as representing the best that can be obtained by modern surgical methods associated with a high degree of surgical skill.

It is significant that over a period of 28 years this distinguished surgeon of high repute had performed the radical operation only 483 times. He states that on the average his operability percentage was 63, in other words 37 per cent of his cases required some other form of treatment than surgical. His total five-year operative salvage of all cases seen was 24.6 per cent.

In 1898, about the time that Ries, Clark, Wertheim and others were devising more and more radical operative procedures, the Curies announced in Paris their discovery of radium. This event regarded at the time as of outstanding scientific importance, ultimately became of the utmost significance in the world of medicine. Three years earlier the roentgen ray had been discovered.

Both radium and roentgen rays were promptly and enthusiastically subjected to rigid scientific study and experiment. In a short time as Burnam says "the relationship between the artificially produced roentgen rays and the spontaneously emitted radium rays, suspected from the beginning, had been adequately proved."

Many chemical and biologic investigations, especially those dealing with the effects of the new rays on living matter were soon published. Outstanding among these investigators was Dominici, whose studies of the histologic changes observed after irradiation in normal and neoplastic tissues established a solid groundwork for the views held today. He concluded according to Burnam "that the tolerance to rays was definitely associated and proportional to the approach to complete adult and highly differentiated states, and that the more undifferentiated and embryonic the tissues were, the less their capacity to tolerate radiation and, conversely, the greater their sensitivity to injury."

By 1909 radium was in use clinically for the treatment of many neoplastic conditions, including uterine and cervical cancers. Its palliative effects in controlling hemorrhage, discharge, and pain were fully recognized. However, with the exception of a small amount of radium in the possession of Dr. Robert Abbè, a New York surgeon, there was little or none available for clinical use in this country.

It was particularly fitting therefore that the pioneer in exploiting the clinical application of radium rays in the treatment of human cancer in America should be one of its outstanding teachers, and

gynecologists, Dr. Howard A. Kelly, a distinguished surgeon and technician, Professor of Gynecology at the Johns Hopkins Medical School.

As more and more experience was gained by clinicians throughout the world in radiation therapy, it became evident that the old conception of cancer as a single disease must be changed. It soon was realized that cancers grossly similar and, apparently identical, often behaved quite differently under irradiation. These observations led to an appreciation of Dominie's earlier histologic studies and a realization that a new classification of cancers could be made based largely on their response to radium or roentgen rays. In other words, some cancers located in certain parts of the body or possessing a certain type of histologic structure might be radiosensitive and thereby would tend to disappear more or less completely and permanently under irradiation. Cancers which failed to show much response to radiation were designated radioresistant.

Gynecologists were among the first to use radium for the treatment of internal cancer, especially cancer of the cervix, as so many of the patients were in an advanced stage of disease when first seen, and even a radical Wertheim operation seemed inadvisable. Soon it was recognized that cancers of the cervix responded quite well to radiation therapy and on the whole must be regarded as radiation sensitive.

In the meantime Broders and others published classifications of epidermoid carcinoma in which the cases were divided into three grades, depending upon variations in histologic structure. The degree of histologic malignancy in these tumors was lowest in Grade I and highest in Grade III. Studies began to appear from radiation therapists, indicating that the radiation sensitivity of the epidermoid tumors, and especially the cervical carcinomas, was lowest in the fully differentiated Grade I cancers and highest in the most malignant or Grade III varieties, so that radiation therapists were able to obtain equally as good end results in the treatment of their cases regardless of the histologic grade of malignancy; whereas studies of large series of patients treated by operation alone, in such outstanding institutions as Johns Hopkins Hospital and the Mayo Clinic, indicated that those patients with cervical cancers in Grade II and Grade III seldom survive five years.

It is quite evident that the entire picture of carcinoma of the cervix histologically, clinically, and therapeutically, as we understand it today, has been created by the discovery of radium and the subsequent developments in the field of radiotherapy. An individual surgeon here or there may still adhere to surgical measures, but throughout the world and especially in all large teaching centers where modern methods of radiation therapy are available they have displaced surgery in the treatment of carcinoma of the cervix. The reasons are obvious:

1. Radiation methods are applicable to all cases.

2. End results or percentage of cures in favorable cases are superior to those obtained by operation.

3. Primary mortality under radiation should not exceed 1 per cent for all types of cases, whereas primary surgical mortality is from 10 per cent to 20 per cent in the favorable cases, treated by the Wertheim operation.

4. Not over 25 per cent of the cases of cervical cancer can be regarded as favorable for surgical intervention. This makes it difficult for more than a very few surgeons to attain the operative skill necessary to perform successfully the radical operation, but unfortunately not all of the favorable cases could reach such surgeons.

5. In the past twenty-five years, the teaching and training of radiologists has progressed with unparalleled speed so that there are special societies with large membership rolls, sections of the state and national societies, a radiologic examining board and also a College of Radiology.

6. As a result radiologists competent to treat the early or favorable as well as the advanced or hopeless case of cervical cancer are to be found in almost every community. It may not be amiss at this point to quote from the closing remarks of Mr. Bonney in the discussion of his paper referred to above: "One cannot look into the future, but I think it is quite possible that we shall one day see the end of surgery as a treatment of carcinoma of the cervix."

Carcinoma of the uterine body likewise has presented a fertile field for radiation therapy. In the beginning there was considerable opposition to its use as it was felt that surgical procedures were in themselves adequate to care for the disease, and besides there was a strong feeling supported by many investigators that adenocarcinoma was not a radiosensitive tumor. However, since carcinoma of the uterine body is a post-menopausal disease, many of the patients were old or feeble, therefore poor risks for major surgery, and other patients declined operation. Radium alone or combined with roentgen ray was the only form of therapy available for such cases and in many instances was used. As a result, considerable evidence gradually accumulated to indicate that radiation methods could establish in carcinoma of the corpus not only palliation of symptoms but permanent cure of the cancer.

Even more significant was the information obtained by studying the histologic structure of the tumors and comparing this with the response to the rays. As in carcinoma of the cervix, it was found that certain types were more sensitive and others more resistant. The less differentiated and more malignant the cell structure the more radiation sensitive the tumor often seemed.

Critical studies of series of cases of cancer of the corpus treated by radiation and surgery seemed to indicate that there are two major histologic groups, one of rather low malignant quality known as adenoma malignum in which panhysterectomy by the vaginal or abdominal route may be expected to establish a permanent cure. The

other of higher malignant histologic character in which hysterectomy gives poorer end results than when radiation alone is used or radiation followed by hysterectomy.

It would appear therefore that the discovery of radium in 1898 by the Curies has changed for the better the entire therapeutic picture in uterine cancer and has to a large extent displaced or superseded surgical measures in the treatment of cancer of the cervix.

This situation has compelled gynecologists to acquire a knowledge of radiation and radiation methods as applied to the treatment of uterine cancer. As a result many gynecologic clinics have assigned one or more members of their staff to the care of the malignant tumor cases, and these individuals have taken special courses and undergone special training for this purpose. It is highly desirable that all patients suffering from uterine cancer, either of the corpus or cervix, should remain under the supervision of the gynecologist throughout their course of radiation therapy, since the complications that may occur almost invariably require surgical attention. In other words, the gynecologist should always assume full responsibility for his patients' care and carry out the radiation therapy if he is, by training, competent to do so. If not he should work in close cooperation with an expert radiologist.

## PUERPERAL INFECTION

B. P. WATSON, M.D. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., F.R.C.O. & G.,  
NEW YORK, N. Y.

THE last twenty years have been marked by notable advances in our knowledge of puerperal infections. These have resulted in a better understanding of the underlying factors leading to infection, of the behavior of the infecting organisms, and of methods of treatment. Already this added knowledge has led to the practical result of lowering both the incidence and the case mortality of the disease.

Twenty years ago it was recognized that the aerobic hemolytic streptococcus was only one of the organisms which might cause puerperal infection, that other organisms were responsible for many cases, and that among these the anaerobic streptococcus played an important role. It is during this period, however, that the two types of infection have been clearly defined and differentiated.

It is forty-five years since Kroenig first described a case of puerperal infection from which he recovered an anaerobic streptococcus. In 1910 Schottmüller described similar cases and named the organism *Streptococcus putridus*. In 1921 Curtis found these organisms in certain cases of pyosalpinx. Then came a series of observations of Schwarz and Dieckmann, and by Harris and Brown in this country, and later by Colebrook in England, confirming the part played by the anaerobic streptococcus in puerperal infection. Schottmüller had already described the characteristic clinical picture: Irregular fever, fetid lochia, thrombophlebitis, not infrequently positive blood culture, occasionally lung abscess. As anaerobic cultures have become a routine in the investigation of cases of fever in the puerperium, it has become evident that a majority of these cases are due to the anaerobic organism. Studies show that this type of infection is most likely to supervene in patients whose tissues had been much traumatized by the delivery, who have lost much blood, who are shocked, or who have had ruptured membranes a long time prior to delivery. It is now known that the infection is practically always an endogenous one, that the organisms exist in the vagina previous to delivery, that they are ordinarily innocuous to the individual, and that it is only under the conditions above mentioned that they are liable to lose their saprophytic character and become pathogenic.

These facts have given us a definite scheme of prophylaxis, viz., the avoidance in every way possible of the long labor, of the traumatization of tissue by forceful vaginal delivery, of excessive blood loss, and, if this is unavoidable, its immediate treatment by blood transfusion. Delay in the performance of cesarean section after labor has begun or the membranes have ruptured predisposes to this type of infection.

The role of vaginal antiseptics during labor is still a matter of doubt. There are those who believe that they may be effective but the majority

of those who have investigated the matter are frankly skeptical. Indeed Colebrook has gone so far as to state that after the use of vaginal antiseptics the vaginal flora is actually increased.

So far no specific drug has been found which will act on this organism as does sulphanilamide on the hemolytic streptococcus, but the progress made in the discovery of variants of sulphanilamide which are effective against other organisms holds out hope that one may yet be found which is more or less specific against these anaerobes.

It is now established beyond a doubt that the anaerobic streptococcus is the most frequent organism present in cases of septic incomplete abortion. This has led to a modification in the treatment of these cases in the last few years. Twenty years ago most of us advocated and practiced ultraconservatism in the treatment of these cases, recognizing excessive hemorrhage as practically the only indication for the emptying of the uterus in the presence of fever. Today a large number of clinics are carrying out prompt evacuation of the putrid uterine contents as soon as culture has demonstrated the absence of a hemolytic streptococcus. The result has been a great curtailment in the duration of the fever and a marked shortening of the time of hospitalization of the patients, with no added mortality.

Our knowledge of the aerobic hemolytic streptococcus has been enormously extended in the last twenty years. This type of infection was the first definitely established on a scientific basis. It may be recalled that micro-organisms were first demonstrated in the lochia of infected women by Meyerhöfer in 1863, and in the blood of infected women by Coze and Feltz in 1869. They described the organism as a coccus occurring in chains. Ten years later Pasteur with his collaborators cultivated these organisms and definitely determined that they were the cause of the infection. For many years thereafter it was thought that this streptococcus was the sole cause of puerperal infection and that it was a specific organism with no variants. Over thirty years ago bacteriologists began to recognize that the aerobic streptococcus could be divided into a series of groups. One of the most important of these subdivisions was that which differentiated between the hemolytic and the nonhemolytic organism. It was at the same time proved that the hemolytic organism was the more virulent of the two. For many years thereafter there was no differentiation of the hemolytic organisms; all were regarded as pathogenic in the human subject. Then came the work of Lancefield and others, who showed that the hemolytic organisms could be differentiated into several groups which were named A, B, C, D, etc. All of these strains may be recovered from the human subject but only those belonging to Group A cause serious infection. This hemolytic streptococcus Group A is now recognized as the organism responsible for a great variety of diseases, including puerperal sepsis. It is the organism responsible for the great epidemics of the past, and for the sporadic cases and minor epidemics which still occur today.

Infection with the Group A beta hemolytic streptococcus is practically always exogenous in origin in contrast to infection with the anaerobic streptococcus which is practically always endogenous. Prior

to the Lancefield classification clinicians were puzzled by the fact that in about 3 per cent of women a hemolytic streptococcus could be recovered from the vagina or cervix in the later part of pregnancy and in labor, and that practically none of those women ever exhibited symptoms of infection in the puerperium. It was thought that these women had acquired an immunity to their own organisms. In the last five years investigation of these vaginal streptococci, by the Lancefield and other techniques, has shown that these organisms do not belong to Group A and are, therefore, really nonpathogenic for all human beings. Since typing of these vaginal streptococci has been systematically done in our Service, not a single Group A organism has been found. It must, therefore, be concluded that in the vast majority of cases of streptococcal infection the organism is introduced from without. Since the streptococcus responsible for puerperal infection is the same organism that causes other varieties of disease such as tonsillitis, otitis media, pneumonia, erysipelas, scarlet fever, etc., it is evident that the parturient and puerperal woman may be infected by contact, either direct or indirect, with such cases. That the infection is usually carried indirectly through "carriers" has been definitely proved. These carriers may or may not have been in contact with infected patients, usually they have not. The organism is most commonly present in their mouths, throats, or noses, and is, apparently, harmless to the individual. As in the case of the vaginal streptococcus, that found in the throat may be other than Group A and, therefore, harmless. Of 103 students examined during the past year, 17 proved to have streptococci in the throat or nose but only one of these was in Group A. Of 242 nurses examined, 30 showed hemolytic streptococci and only 3 of these belonged to Group A.

One of the first to call attention to the importance of the carrier was Meleney, who in 1926 showed that a series of streptococcal infections in surgical wards was traceable to certain streptococcal carriers in the operating room.

Two years later, in the Sloane epidemic of 1927, he proved that organisms of infected patients were serologically identical with those recovered from the nose and throat of certain individuals of the nursing and medical staffs. Since then a mass of evidence has accumulated, definitely establishing this relationship between carrier and patient. One of the most notable observations was that conducted by Kinloch, Smith, and Stephen in Aberdeen. This knowledge has made possible a most important prophylaxis against this type of infection, namely, the exclusion from contact with parturient or puerperal women of all such carriers. The detection of these carriers involves regular periodic cultures of the nose and throat of each attendant and the exclusion of individuals who prove to be positive. As an additional safeguard, the complete masking of the nose and throat of doctors, nurses, and attendants on the parturient and puerperal patient is essential. This technique is now carried out in every well-conducted clinic in the country and must be responsible for a diminution in the incidence of infection.

In the Sloane epidemic of 1927, the noses and throats of the carriers were the only sites in the environment of the infected patient from which organisms were recovered. It was, therefore, concluded that the organism would not survive for any length of time outside the human body.

Some years later, however, Dr. Elizabeth White, working with Colebrook at Queen Charlotte's Hospital in London, recovered the organisms from the dust of rooms occupied by infected individuals, and this even after a considerable period of time had elapsed since the patient was removed from the room. Her findings have been confirmed. This fact has re-emphasized the great importance of complete isolation of infected individuals and of thorough disinfection of the rooms which they have occupied and also of the contents of the rooms. It has re-emphasized the necessity for a separate and distinct isolation unit in every maternity service; the danger to obstetric patients if they are delivered in a room where general surgical work is done, and the danger to which the puerperal patient may be exposed if she convalesces in a ward or room in the immediate vicinity of infected individuals.

The detection of a single case of hemolytic streptococcal infection now calls for immediate and complete isolation of that individual and a thorough bacteriologic examination of everyone who may have come in contact with her. If such precautions are taken, no epidemic of any major character should be possible in the future. Our own experience is that hemolytic streptococcal puerperal infection is a rarity today, and we cannot but believe that the lowered incidence, as compared with twenty years ago, is, at least partly, due to these simple precautions.

Along with these advances in prophylaxis has come a most notable addition to the treatment of the disease. It is just five years since prontosil was demonstrated to have a notable effect in experimental, hemolytic streptococcal infections in mice. This observation was made by Domagk, in Germany. One of the first to follow up this observation in clinical work was Colebrook in London. He administered prontosil to patients with hemolytic streptococcal infection with startlingly beneficial results. Since then it has been demonstrated that sulphanilamide, a derivative of the original prontosil, has a profound effect on all types of hemolytic streptococcal infections, of which puerperal infection is just one. As with all new remedies its use has been rather indiscriminate. The rational mode of employment would seem to be to administer it to every patient with definite evidence of puerperal infection, to take cultures immediately and only continue the drug if a hemolytic staphylococcus, *Bacillus coli*, or gonococcus is found to be present. In cases of a staphylococcal infection sulphathiazole has been found to be effective. The advances made in chemotherapy for infections have been so spectacular in the past five years that there appears to be ground for hope that still further progress will be made in the immediate future. In connection with therapy, mention must be made of blood transfusion. Twenty years ago blood transfusion was still regarded as something to resort to only when all else had failed. Today

it is a standard method of treatment for all types of puerperal infection and is used from the onset of the disease. There can be no doubt as to its beneficial results when so employed.

To sum up we may say that in the last twenty years definite advance has been made along the following lines:

1. Recognition of the part played by the anaerobes in puerperal and postabortal infection.
2. Proof that these anaerobic infections are endogenous in origin.
3. Proof that such infections are predisposed to by shock, hemorrhage, prolonged labor, and traumatization of tissue.
4. Realization that the removal of dead and decomposing material resulting from this type of infection can, in most instances, be effected with no risk, and usually with great benefit to the patient.
5. Identification of different groups of the beta hemolytic streptococcus and proof that only Group A is virulent in the human subject.
6. Establishment of the fact that infection with this organism is practically always exogenous.
7. Proof that these organisms are usually conveyed to the patient by a carrier who harbors them in mouth, nose, or throat.
8. Demonstration of the fact that the risk of infecting patients is practically annulled by periodic nose and throat culture of all the members of the obstetric staff and elimination of those who are carriers, and by the complete masking of the nose and mouth of all those who are attendant upon the parturient and puerperal woman.
9. Demonstration of the persistence of the organisms in the environment of an infected individual even for long periods after her removal therefrom.
10. A recognition of the necessity for most complete isolation of all such infected individuals and for proper provision for this in every maternity service.
11. The discovery of the beneficial effects of sulphanilamide and its derivatives in streptococcal, gonococcal, and *Bacillus coli* infections.

## THE MANAGEMENT OF THE MENOPAUSE

EMIL NOVAK, M.D., BALTIMORE, MD.

WE HAVE learned much within the past generation as to the physiology, and especially the endocrinology, of the reproductive cycle, and this new knowledge has given us a better understanding of the nature and significance of menstruation and the various menstrual disorders, including also the menopause. Inevitably, though slowly, a smattering of this newer viewpoint has seeped through to the laity, so that the folklore concepts of a former day are less generally prevalent than they once were. To say that they have been dissipated would be glaringly incorrect, as every practicing physician knows. For example, there are still many women, not always of the ignorant group, who believe that the "change of life" entails a profound change in their life activities, and that the woman must at this dreaded epoch run the gauntlet of certain grim specters, such as mental breakdown, cancer, and the loss of sex attractiveness to her husband.

Even women who are better informed are wont to ascribe almost any subjective symptom which occurs after the age of forty to the oncoming menopause, and it cannot be fairly denied that some of our own profession innocently foster such wrong ideas by too ready acquiescence in such explanations. Too often it is an easy way out in the management of troublesome headaches, vertigo, nervous instability, anxiety neuroses of one sort or another, and many other symptoms which may have no relation whatsoever to the menopause. The woman who begins at the age of forty to excuse her vagaries on the "change of life" basis may not cease to menstruate until the age of fifty, this constituting a fairly effective refutation of her hypothesis.

There can be no doubt that in dealing with women as a whole we must take cognizance of this still heavy substratum of wrong concepts as to the significance of the menopause. The practical point from the physician's standpoint is that the easy assumption of menopausal etiology of symptoms in women of the fifth decade of life may lead him to overlook the real cause of these symptoms. Often they are explainable more rationally as the result of the stress and strain resulting from the rearing of large families of children, or because of domestic, economic, or marital problems, sometimes because of genuine physical disease. To give such a woman "shots" of estrogenic substance is a short cut for the doctor, but it is quite sure to bring the woman little relief in her difficulties.

But there are other wrong concepts, and other possibilities of mismanagement which may even spell death to the woman. The most glaring example is the belief of many women that abnormally excessive or irregular menstruation is to be looked upon as a normal manifestation of the menopause. This prevalent fallacy has been the direct cause of death for innumerable women, as every gynecologist will be

willing to testify. Education on this point is a vital necessity in the campaign against cancer of the uterus, a campaign in which every practitioner can play a part.

So far, I have said nothing as to the most characteristic of all menopausal symptoms, and, in fact, the only ones whose menopausal genesis will be conceded by all. I refer to the vasomotor group of symptoms, embracing the typical hot flushes which characteristically involve the head, neck, and the upper part of the thorax; the less frequent hot flushes which may involve the whole body; and the frequent sweats, which usually, but not always, are associated with the flushes, which they not infrequently immediately follow. This group of symptoms is definitely objective. The flushes, for example, can be seen and counted. They are definitely due to the hormone changes which characterize the menopause, although even these symptoms are influenced to some extent by emotional and psychic factors, through the link-up between the endocrines and the higher centers.

On the whole, however, these vasomotor symptoms offer the best criterion as to the severity of the climacteric and as to the efficacy or inefficacy of therapeutic measures. For the average practitioner, they will serve as a more readily available guide to therapy than the study of vaginal smears, useful though the latter may be to those taking the trouble to familiarize themselves with the comparatively simple technique.

So much stress has been placed by some upon the control of therapy by vaginal smears that the average practitioner is likely to believe that this procedure is essential to the intelligent management of the menopause, which I do not believe to be the case. It should be remembered, also, that there is no essential parallelism between the character of the vaginal smear and the degree of relief afforded by estrogenic therapy. For example, the symptoms are not infrequently relieved when there is little or no change in the smear.

Aside from the vasomotor phenomena, there is little doubt that the endocrine readjustment of the menopause may in some cases be the direct cause of such symptoms as headache, vertigo, and nervous instability. More often, however, the latter would seem to be of secondary nature. If, for example, a woman approaches the menopausal era with apprehensiveness, and if she begins to experience vasomotor symptoms which often disturb her rest at night, what is more natural than that she should become irritable and depressed, and develop headache and other symptoms, just as she would with any functional nervous disturbance. When the headaches are definitely periodic, occurring just before or during a menstrual period if the woman is still menstruating, or at approximately four-week intervals, if the periods are skipped or have ceased entirely, the evidence for an endocrine (pituitary) origin is much stronger, and headaches of this sort are almost always amenable to adequate estrogenic therapy.

The immediate cause of the menopause is a cessation of ovarian function. This statement can be made without equivocation now, although at one time it was thought possible that the explanation might lie in the fact that the cessation of ovarian function might be merely sec-

ondary to cessation of pituitary function. However, it is now established that the break in the endocrine chain occurs primarily in the ovary. The latter, in other words, reaches the end of its functional life span at the menopause, and beyond this is refractory to any form of pituitary stimulus.

Since the pituitary continues to function beyond the menopause, it would be expected that the characteristic hormone changes of the menopause, as determined for example by assay of the urinary hormones, would be a disappearance of estrogenic hormones and an excess of the gonadotropic principles, and this is exactly what occurs. The gonadotropic excess is demonstrable for many years beyond the menopause, the follicle-ripening principle predominating, but the luteinizing hormone has also been demonstrated in some cases. The disappearance of estrogen is not invariable, and this hormone has been found in the urine of some women long after castration. The postmenopausal occurrence of estrogen has not yet been satisfactorily explained. Some believe its source to be in certain chemical metabolites of the sterol group of substances, but there is more reason to believe that some other endocrine gland, most likely the adrenal cortex, may play an estrogenic role after the menopause.

In any event, the menopausal symptoms are due to the disruption of the previously reciprocal interaction of the pituitary and ovaries. Just how this brings about the symptoms we cannot say. There is increasing evidence of a close liaison between the endocrine system and the higher centers, particularly in the region of the pituitary, though no one can speak with precision as to the pathways involved. The menopausal flushes in many ways resemble physiologically the vasomotor phenomenon of blushing, but just how the endocrine disturbance is translated to the vasomotor apparatus, and why the unpleasant symptoms disappear after a time, even though the endocrine imbalance still apparently persists, no one can say.

The bearing of menopausal hormonology upon the endocrine treatment of climacteric symptoms is obvious. The rationale of estrogenic therapy seems clear, and is now universally accepted. Such treatment substitutes for the lack of the patient's own estrogen, letting her down more gently and gradually in this transition period, and removing temporarily the immediate cause of the symptoms. Even those who are inclined to ascribe the symptoms to the gonadotropic excess rather than to the estrogen deficiency will agree that the best hormonal means of inhibiting excessive gonadotropic function is through the administration of sufficiently large amounts of estrogen, a principle which we utilize in the treatment of various gynecologic functional disorders.

All this may seem at first sight to have moved us in a circle to that day, nearly a half century ago, when ovarian therapy was first begun in the treatment of ovarian deficiency disorders, practiced thereafter with enthusiasm by some and ridiculed by others, until the more accurate knowledge of recent years has unified gynecologists as to the value of the ovarian therapy of today in the treatment of menopausal symptoms. A backward glance over the years fully justifies the hard-boiled skeptics who believed that the ovarian therapy available for the

first two decades of the present century was of little or no value except for its psychic effect upon the patient. This method of treatment was begun at the old Landau clinie in Berlin in 1896, simply on the basis of an assumed analogy with the thyroid; for some years previously Murray and others had shown the brilliant results of thyroid therapy in the treatment of thyroid deficiency states. Curiously enough, at this time there was no knowledge of an internal secretory function of the ovary. But the great wave of ovarian therapy had been started, and billions of expensive tablets and capsules of ovarian substance were consumed by millions of trusting women in these early days of organotherapy enthusiasm. And now we know that these various organ extracts were inert or, at best, that they contained only negligible quantities of the ovarian hormones. It is a sad commentary on our profession that even our high-grade pharmaceutical houses feel it necessary still to continue the manufacture of these same old preparations today, simply because they are still prescribed by many of our profession.

For this practice there would seem to be no excuse today, since we now have available preparations of both ovarian hormones, and since these are unquestionably potent both experimentally and clinically. The advance in this field has been a very genuine one. The exact composition of both ovarian hormones is known; they can be prepared synthetically; they can be isolated in crystalline form; and we have learned much concerning their physiologic effects. In short, we can handle them just as we do the better understood drugs. Moreover, most of the estrogenic preparations on the market are trustworthy, in that they contain what they purport to contain. Why any physician can still cling to the use of the older forms of ovarian or corpus luteum tablets is difficult to understand, and more difficult to justify.

With reference to the methods of estrogenic therapy in menopausal cases, the first point meriting emphasis is that the great majority of menopausal women require no endocrine treatment at all. Many a woman passes through the menopause without "batting an eye," others have only mild vasomotor symptoms, and only a comparatively small proportion are made so miserable that endocrine therapy is necessary for relief. It is obvious that the mental attitude of the patient and the degree of endocrine enthusiasm of the attending physician will influence the frequency with which hormone treatment is resorted to. I have already stressed the very great importance of reassuring the patient and explaining to her in simple language what the menopause means and what it does not mean, as well as of correcting so far as possible any detrimental environmental factors which may exist.

In the minority of cases in which vasomotor symptoms are very severe, in which, for example, flushes and sweats occur fifteen or twenty times a day and so frequently during the night that the patient's rest is seriously disturbed, my experience is that nothing yields such beneficial results as estrogenic therapy by the hypodermic (intramuscular) route. The dosage must be adjusted according to the severity of the symptoms and the degree of response. In a case of average severity an injection of 10,000 international units of a good estrogenic

preparation in oil is given every third day for from two or three to as many as six or eight injections. Usually the symptoms are so ameliorated after a few injections that the latter may be stopped. In some cases smaller dosage will suffice. The quantitative relationships vary so much in different women that the effective dose must also vary, aside from the varying severity of the symptoms.

In the interval between exacerbations, which have a tendency in many cases to occur at approximately four-weekly intervals, the patient can be kept quite comfortable by one of the oral estrogenic preparations, for estrogen is effective when given by mouth. However, the dosage required for the same effect is many times (estimated variously at from five to a hundred) that necessary for the hypodermic route. It is true that the latter is more disagreeable to the patient, but it is, in my opinion, so much more effective in the severe cases that it is to be preferred. The objection urged by some that the vegetable oil in which the hormone is dissolved often remains to form a painful nodule is not confirmed by my own experience. In mild cases, or in the intervals between severe exacerbations, the oral method would naturally be preferred. It is clear, therefore, that even in those women who suffer a severe and prolonged menopause, constant hypodermic medication is not required, and by a combination of the hypodermic and the oral routes almost all patients can be kept reasonably comfortable. Again, it should be emphasized that active endocrine therapy of this sort is necessary in only a small proportion of menopausal women. The great majority of women at this epoch require no treatment at all, or only such simple measures as reassurance and perhaps the employment from time to time of simple nerve sedatives, such as the barbiturates.

The question is often asked as to whether or not the prolonged use of estrogens can produce harmful results, especially in predisposing to the development of cancer. The relation between estrogenic and carcinogenic substances has been in the forefront of discussion for several years, and the question is too big a one to elaborate in this paper. Suffice it to say that there is as yet no worthwhile evidence to indicate that even large therapeutic doses of estrogen, far larger than are necessary in menopausal cases, carry with them any risk of inciting cancer. The experimental production of cancer in certain animals by means of estrogen injection has been possible only through the prolonged use of huge doses, many times as large as would ever be justified therapeutically, and in animals of a cancer-susceptible strain.

Granting all this, however, we must remember that certain human beings are quite certainly also unusually cancer susceptible, so that, even in the absence of convincing direct evidence on this point, the theoretical possibility of exciting such a latent tendency through excessive estrogenic therapy cannot be excluded. In the present state of the question, there is certainly no justification for withholding proper estrogenic therapy when menopausal symptoms are troublesome, with the reservation that excessive or unusually prolonged treat-

ment be avoided as far as possible, particularly in women who because of hereditary or other factors might be expected to belong to the cancer-susceptible group.

There is no doubt that the estrogens have often been used in unnecessarily large doses and in an indiscriminating way. When this occurs at the menopause, uterine bleeding may be provoked. This may be a disturbing complication when it occurs many months or even several years after the cessation of the menstrual function, as it raises the possibility of intrauterine adenocarcinoma, and may call for diagnostic curettage to eliminate this possibility. I have recently seen such bleeding in a woman who had been given an average weekly dose of 100,000 international units for several months. Incidentally, the history of this patient led me to believe that there had been no indication for any estrogenic treatment whatsoever.

Finally, no discussion of menopausal therapy would be complete without some mention of the nonhormonal estrogenic substances which for the past two years or so have been employed in an experimental way as substitutes for the natural or synthetic hormones. The chief representative of this group of substances is the stilbene derivative known as stilbestrol. Its chemical structure is not in any way like that of any of the estrogens, and yet it has powerful estrogenic activity, more marked, indeed, than the natural hormone derivatives themselves. While not available commercially, the experimental clinical study of stilbestrol which has been made in many clinics has led to practically unanimous agreement as to its estrogenic potency. Unfortunately, however, it possesses the serious disadvantage of a considerable degree of toxicity, many patients being unable to take it because of nausea, vomiting, vertigo, and other unpleasant symptoms. The incidence of such toxic effects has varied widely in different reports between such extreme limits as 10 per cent and 80 per cent.

Moreover, it is still too early to be sure whether long-continued use of stilbestrol carries with it any more serious danger than the comparatively mild and apparently very temporary toxic effects which have thus far been noted. Work along this line is being pushed, and it seems reasonably certain that sooner or later a simple estrogenic chemical will be evolved which will be free of the toxic properties of stilbestrol. The inexpensiveness of such chemicals as compared to the high cost of hormone preparations will make this a real boon. In the meantime those who employ stilbestrol should be cautious in the matter of dosage, and should be on the alert for symptoms of toxicity. My experience has led me to feel that the daily oral dose in menopausal cases should rarely if ever be over 1 mg.

It would be beyond the limits of a paper of considerate length to include a discussion of certain pathologic manifestations which may be noted at the climacteric, such as (1) involutional melancholia, which gynecologists see far more rarely than do institutional psychiatrists, and which is probably less intimately linked up with the cessation of ovarian function than some would have us believe; (2) the so-called climacteric arthritis, concerning which there is also some question, but which does seem related to this epoch, being characterized most often

by pain and swelling of the knees, with often rather typical supracondyloid tenderness; (3) the moderate climacteric hypertension, often of fluctuating type, which many have noted at, and just after, the menopause, and which is likely to be transient and apparently favorably influenced by estrogenic therapy; (4) functional uterine bleeding, an exceedingly common but easily curable gynecologic disorder of this life period.

#### SUMMARY

In spite of a healthier attitude among women in general as to the significance of the menopause, there is still a considerable substratum of misconceptions on this point, and the physician must take cognizance of this in the management of climacteric women. The majority of women at this phase need no treatment at all, many require only reassurance and education, and in only a comparatively small proportion is ovarian endocrine therapy necessary. There is perhaps no gynecologic disorder in which the indication for organotherapy is more rational than in the treatment of typical climacteric symptoms, especially the vasomotor group. There is a definite field for both the parenteral and oral routes of administration of the estrogenic hormones, the former being much more effective when the symptoms are severe.

On the other hand, it must be remembered that many symptoms frequently observed in menopausal women are not directly due to the endocrine readjustments of this period, but that they are more logically explained as due to environmental and psychogenic factors of one sort or another. The physician who depends upon endocrine therapy alone will fall short of the requirements in many cases, and indiscriminate estrogenic therapy should certainly be frowned upon.

The question of the possible hazard of inciting malignancy in cancer-susceptible individuals cannot be decided too arbitrarily in the present state of our knowledge, though it is fair to state that no impressive evidence of such a danger has as yet been adduced, after many years of employment of the method. Certainly it would at the present time be carrying conservatism and caution to an extreme to deprive the menopausal woman of proper estrogen therapy when this is otherwise indicated, merely on the basis of this slight theoretical possibility.

Stilbestrol, because of its high degree of estrogenic activity, is very effective in the control of menopausal symptoms, but its use carries with it the disadvantage of toxicity in a considerable proportion of cases, in my own experience about 20 per cent. While these are practically always mild and while they disappear with cessation of the drug, their occurrence makes it inadvisable to release the preparation for general clinical use, especially in view of the uncertainty as to the possible effects of its long-continued use. The dosage should be kept at the lowest effective level, and it is only rarely necessary to employ more than 1 mg. daily.

## PREGNANCY AND DISEASE

HUGO EHRENFEST, M.D., ST. LOUIS, MO.

WITHIN the last two decades a great deal of new information has become available in regard to certain biochemical and functional alterations typically occurring all through the maternal organism under the influence of a normal pregnancy. Careful study and judicious interpretation of all these manifold changes justify the conclusion that they serve a rational purpose and in the last analysis accrue to the benefit of the fetus in utero. The fact that identical, or at least very similar, alterations to a limited degree are also found in the premenstrual phase must be accepted practically as proof for the modern conception of menstrual function as periodic, local, and systemic preparation of woman for a pregnancy. Indeed, the premenstrual structural modifications of the endometrium are now customarily designated as "pregestational" or "pregravid."

With the onset of pregnancy, that is with the realization of the merely anticipated implantation of a fertilized ovum, these characteristic, local and systemic premenstrual changes not only persist but immediately become intensified. We may well say that while the premenstrual changes solely express *qualitative* requirements, they adapt themselves with the onset of pregnancy to actual *quantitative* needs. This biologic adjustment of the entire body occurs in response to specific stimulation by definite hormones, which during pregnancy, as we at present believe, are chiefly elaborated by chorionic tissue.

Normal physiologic pregnancy reactions in general imply an increase both in functional ability and functional activity of various organs and organ systems. As a whole, this effect proves advantageous and usually results in some permanent benefit. Clinical experience shows that, as a rule, a woman at the start of her second pregnancy proves biologically better equipped for gestation.

Reproduction represents the maximum of physiologic ability of woman and therefore necessarily calls for maximal functional activity of practically all her organs. While admittedly lying within the limits of physiologic normality, the morphologic, chemie, functional, static, and emotional alterations brought on by pregnancy often will give rise to clinical manifestations which in a nonpregnant individual always would indicate a truly pathologic condition.

The feeling of well-being is determined by an harmonious interaction of all organic functions under control of the autonomic nervous system. This equilibrium is likely to become disturbed, at least temporarily, at the onset of pregnancy, if with the sudden call for greatly increased activity some of the important vital organs fail to respond promptly or adequately. The molimina of early pregnancy, with relatively rare exceptions, subside or disappear completely within the first twelve weeks. The disturbed equilibrium evidently has been restored.

In the constitutionally normal and healthy woman, the adequate adjustment to greatly augmented functional demands is facilitated by the fact that in a normal individual all the organs participating in vital functions evidently are endowed with a physiologic reserve available for emergency.

This important reserve endowment, however, will be limited or entirely absent in women who may be classified as constitutionally deficient. In some of them, certain organs or organ functions may not have fully developed through premature arrest in normal postfetal development; in others, they may have become damaged by disease, often during childhood. In such individuals the actually present functional limitations frequently remain unnoticed under a normal mode of life. They manifest themselves only with the onset of a pregnancy, and then response to increased demands is slow or insufficient. Under the strain of enforced overactivity, which increases as pregnancy advances, in such primarily only functionally deficient organs, morphologic changes of a definitely pathologic nature are likely to develop. Signs of seemingly only transient inadequacy may thus during pregnancy change, often imperceptibly and unexpectedly, into symptoms of actual disease.

Pregnancy by itself must undeniably be accepted as a possible direct factor in the origin of disease; however, with improved antenatal technique and newer methods of dealing with severer disturbances of pregnancy, the belief in the importance of reproduction as a frequent or basic cause of disease has diminished to a noticeable degree. It has become apparent that a medical, mental, and occasionally even a surgical disease, which manifests itself during or soon after pregnancy, more commonly represents the recurrence or acute exacerbation of a pre-existing pathologic condition which had remained latent under the conditions of a normal life.

At the first antenatal examination, made as early as possible, the patient must be questioned in regard to all previous medical, surgical, or mental diseases and symptoms. At this occasion a careful physical examination, which now almost routinely includes a Wassermann or Kahn test, should attempt to ascertain the presence or absence of any maternal disease. There can be noticed an increasing tendency to subject all suspicious cases to a tuberculin test or x-ray study of the chest. Oral examination and inquiry into food habits have become routine with growing appreciation of dental caries and deficiencies in mineral and vitamin intake in the causation of various complications of pregnancy.

Comparatively few diseases preclude the possibility of impregnation, and therefore practically every known disease at some time has been encountered in a pregnant woman.

Such an association of pregnancy with disease can express itself in three possible forms: (1) Disease and pregnancy independently follow their usual course. (2) The coexisting maternal disease affects pregnancy, labor, puerperium, and possibly also the future health of the liveborn infant. (3) An intercurrent impregnation aggravates, but occasionally even improves, the usual course of the associated disease.

In the cases falling into the two last mentioned groups, both frequency and intensity of effects on either pregnancy or disease are chiefly determined by the nature of the disease. A detailed discussion of all these possibilities, of course, becomes impossible within the limits of this mere survey. However, it is possible to discern basic causes for untoward effects of pregnancy and disease on each other which are common to many of the diseases most often encountered in obstetric practice.

#### A. EFFECTS OF MATERNAL DISEASE ON PREGNANCY

1. A fairly frequent consequence is premature expulsion of the uterine contents as a result of primary fetal death. The fetus may fail to obtain a sufficient supply of oxygen (e.g., in advanced pulmonary diseases, chronic or acute; cardiac failure, etc.), or to receive certain nutritive materials in required amounts (marked general debility or exhaustion from various causes). Since the intrauterine temperature is higher than that of the mother, in cases of high fever (especially with sudden rise following chills), the fetus may actually succumb to a heat stroke. Some maternal diseases are transmitted to the fetus by way of the placenta. Viruses and bacterial toxins (smallpox, typhoid, etc.) can pass through the intact placenta. In diseases caused by micro-organisms (syphilis, tuberculosis, malaria, etc.) their transition to the fetus is usually made possible by degenerative processes in the placenta which destroy the normal chorion-epithelial barrier against passage of form elements between maternal and fetal blood. Certain poisonous substances (such as lead, morphine, nicotine) will filter gradually, or suddenly in large amounts, into the fetal blood stream.

2. Premature uterine activity in some instances is due to abnormally increased general nervous irritability. Strong uterine contractions, initiating an abortion or premature labor, are not infrequently observed in connection with excessive intestinal peristalsis brought on by intestinal disease or strong cathartics. Premature uterine activity may follow administration of certain drugs; e.g., ergot or quinine. It must be emphasized, however, that quinine is given in all cases of malaria, because more fetal lives thus are saved through the prevention of further chills.

3. In general, the resistance of the fetus against all unfavorable influences of a concomitant maternal disease increases as pregnancy advances. Therefore, in the later stages of gestation, transition of micro-organisms, viruses, or bacterial toxins (possibly simultaneously with immunizing antibodies) will not necessarily lead to fetal death. Under such conditions, particularly in cases of acute infectious diseases, the liveborn infant can show evidences of the transmitted disease in an active stage (syphilis, smallpox, tuberculosis, occasionally also malaria) or exhibit the proof of recovery from the transmitted disease in form of typical scars (smallpox), or by failing to react to specific vaccination (smallpox) or by yielding (typhoid) a positive Widal reaction. A positive Wassermann reaction will establish the latent stage of transmitted syphilis.

4. Acute infectious and contagious diseases (scarlatina, erysipelas, diphtheria, etc.) are prone to cause serious complications of the puerperal state.

#### B. EFFECTS OF PREGNANCY ON A COEXISTING MATERNAL DISEASE

Mention already has been made of the important fact that both the disease and the pregnancy can, without any noteworthy influence on each other, run their usual courses. As far as such lack of effect on an associated disease is concerned, it holds true for the great majority of cases seen by the obstetrician.

The heretofore widely prevailing belief in inevitable and dangerous consequences of an intercurrent pregnancy on some diseases (especially pulmonary tuberculosis and cardiac disease) is steadily weakening, parallel with an ever increasing conviction that the fate of the sick and pregnant woman is actually determined by proper and adequate treatment of her disease. The present tendency to install maternity departments in all larger tuberculosis sanatoriums is one of the most striking evidences of newer conceptions in regard to appropriate dealing with the disease in a pregnant woman.

Pregnancy and labor are likely to supply some factors which may adversely affect the course of certain maternal diseases. The most common and more important of these factors can be grouped as follows:

1. Exaggerated vomiting may increase the patient's debility and thus lower resistance to the associated disease. Marked malnutrition, starvation, vitamin deficiencies, etc., will aggravate or actually initiate various pathologic conditions.

2. Physiologic, gradually increasing and enforced overactivity of already diseased organs is likely to lead to serious morphologic deterioration with proportionate decrease or almost complete annihilation of their functional abilities. Such consequences occur most often and most markedly in connection with diseases of the kidneys, liver, heart, and lungs. As far as functional anomalies of thyroid or pancreas are concerned, the stimulating effect of an intervening pregnancy or fetal demands, in some instances, may actually improve the patient's condition.

3. Particularly, in the advanced stages of gestation, the large uterine tumor exerts pressure against various abdominal viscera. The possible results are: Reduced amplitude of respiratory movements of the diaphragm, interference with intestinal peristalsis, with passage of urine from kidney to bladder, or with blood circulation. It is obvious that in this manner the course of diseases of the respiratory, gastrointestinal, urinary, or circulatory systems can be adversely affected. This same mechanical effect, however, may prove beneficial, e.g., in a case of marked nephroptosis. It has been claimed by some authorities that the steadyng effect of the large uterine tumor on the diaphragm in some respects resembles the beneficiary effect of artificial pneumothorax or phrenicectomy in cases of acute pulmonary tuberculosis.

4. Among unfavorable influences connected with labor, delivery, and lactation, the most common are: Severe pain, physical exertion, blood

loss, general debility, and shock. Fortunately all these risks can now be greatly reduced, if not fully eliminated, by appropriate obstetric procedures.

The foregoing theoretical considerations of the manifold interrelations between pregnancy and disease can leave no doubt in regard to the significance of prompt diagnosis of a disease accompanying pregnancy. In case of any doubt concerning exact diagnosis and appropriate treatment, the obstetrician, therefore, has learned to appreciate aid from the respective specialist. Most of the larger obstetric services in this country at present include in their regular staffs experts in diseases of the heart, lungs, and kidneys. Incidentally the fact may be emphasized that this cooperation of obstetricians with other specialists in prenatal care has resulted in our present, greatly advanced information concerning the complex interactions between pregnancy and disease.

In this problem there arise still other weighty questions which the attending physician or obstetrician has to answer. Not so rarely he is called upon to make vital decisions in regard to such other closely related problems as *advice against marriage*, *prevention of pregnancy*, or *interruption of pregnancy*. Obviously the answer in each instance will depend chiefly on the nature and state of the particular disease. Nevertheless it is possible to group at least some basic principles for decision which apply to several of the more common diseases.

1. *Advice Against Marriage*.—In some states of this country premarital certification of absence of venereal disease, especially of syphilis, now is legally required. Wider diffusion of present knowledge in the problems of heredity and eugenics plausibly accounts for a noticeable increase in voluntary premarital medical consultations.

Marriage often promises for the woman an improvement in her social-economic condition, which may enable her to nourish herself better, to work less, and even to secure more efficient treatment of her disease.

A strong warning against marriage will always be justified if the woman is suffering from a disease which can be expected to be greatly aggravated by pregnancy; if either man or woman, contemplating marriage, is suffering from a medical, surgical, or mental disease which is prone to lead soon to physical incapacity or death; and if either party has a disease which could, or usually is, transmitted to the offspring, or is likely to disturb or prevent satisfactory and harmonious union in marriage.

2. *Prevention of Pregnancy*.—Obviously, marriage does not necessarily imply the occurrence of pregnancy and thus the possible risks connected with it. The chances of impregnation can be greatly reduced by intelligent and faithful use of some of the methods of contraception now available. They prove particularly useful when prevention of impregnation is desirable or necessary for only a limited period of time. In this respect, under prevailing conditions, the physician also must take into account the social-economic status of the patient. One more pregnancy may not necessarily aggravate seriously the associated disease (a quiescent pulmonary tuberculosis or a compensated heart

lesion), but one more child may well imply hazardous reduction in required rest or even food supply.

Reliable and continuous prevention of pregnancy is clearly indicated, e.g., in advanced cases of tuberculosis, nephritis, cardiac lesions, in instances of associated malignancy and certain forms of mental disease. Permanent sterilization is secured only by operative procedures either on the wife or the husband, which during the last two decades have been almost standardized.

3. *Interruption of Pregnancy.*—Deliberate termination of a pregnancy always is a hazardous operation, and its risks are inordinately increased when done on a seriously sick woman.

Relatively few pathologic conditions still are accepted as definite indications for interruption of pregnancy: laryngeal tuberculosis, otosclerosis, certain forms of insanity. In the majority of instances a decision for termination of pregnancy becomes justified because in spite of appropriate therapy the patient's disease shows evidence of further aggravation.

As emphasized before, prompt and adequate treatment of the associated disease today is generally recognized as the best means of safeguarding the mother, and for this reason the incidence of so-called "therapeutic" or "medicinal" abortions is continuously decreasing, at least in all large obstetric services.

While interruption before viability necessarily means the deliberate sacrifice of the fetus in the interest of the mother, the situation is entirely different when termination of gestation is taken under consideration after fetal development has reached a stage where extrauterine continuation of his life is possible or probable. Under these circumstances premature start of labor may become justified as well in the interest of the child. However, when thus considering and weighing the best interests, both of mother and infant, the most difficult problem for the obstetrician occasionally arises in the decision whether the patient's condition safely permits continuation of gestation until fetal viability is reached. Here again the value of advice from a specialist is obvious.

In this connection a few remarks must be made in regard to cesarean section. Under certain conditions this operation undeniably offers the best chances for both the sick mother and the child. It eliminates several of the special risks of labor and delivery and incidentally offers a ready opportunity of securing permanent sterilization which may be indicated by the complicating disease. However, this latter advantage does not warrant the growing tendency toward performing a cesarean section at or near term simply because sterilization is justified in the particular case.

In concluding this survey I can assert that within the last twenty years our knowledge of the possible influence of pregnancy and disease on each other has been greatly enriched, though it remains wanting in many respects. In medical writings the formerly customary term "pregnancy complicated by disease" is being gradually replaced by the more optimistic phrase "pregnancy associated with disease," which, of course, does not deny the possibility that such association occasion-

ally represents a very serious complication. However, the obstetrician now is less intimidated by the presence of a maternal disease, is less inclined to proceed forthwith with termination of the pregnancy, and exhibits much more interest in the coincident disease.

It is regrettable but probably inevitable that in spite of extensive and careful studies no reliable information, not even in regard to such more common diseases as tuberculosis, nephritis, or cardiac lesions, is available concerning their incidence among pregnant women, their consequences both for mother and fetus, and the best forms of medical and obstetric management. Wide variations and actual contradictions can be noticed in data and conclusions offered by large obstetric services of this and foreign countries. As a matter of fact such statistics are not comparable. The clinic equipped with a staff of experts in various special fields necessarily will show a surprisingly high incidence of associated diseases. The inclusion, in large numbers, of cases discovered in a very early stage is bound to vitiate statistical deductions, e.g., in regard to results obtained with this or that favored method of treatment. This same therapeutic procedure may statistically have proved entirely inadequate in another maternity service which, possibly for solely local reasons, is admitting in an unduly large proportion rather advanced cases of a certain type of disease.

In the individual case the attending obstetrician remains the final judge, but it can be assumed that familiarity with certain basic principles outlined in the foregoing pages will prove helpful to him in making his decision.

## THE PROGRESS OF CESAREAN SECTION

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

THE last twenty years form an important milestone in the development of cesarean section. Previous to 1920, the Sänger or classical cesarean section was usually resorted to and the lower segment operation was but seldom employed. It is during the last two decades that numerous modifications in technique have been elaborated to increase the safety of the latter procedure. A review of the forty volumes of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, from 1920 to 1940, paints a clear picture of the evolution of the low or cervical cesarean sections. Two considerations of cesarean section stand out:

*First, The Living Child.*—From the earliest times the first consideration of cesarean section has been the living child. In the earlier days speed of operating was presumed to be important, for it was thought that the sooner the child was born, the greater were its chances of surviving this method of delivery. With speed in mind it was not uncommon to see the abdomen and uterus opened with one sweep of the knife. Naturally, accidents resulted, such as injuring or cutting the intestine which had found its way in front of the uterus; the placenta was incised if inserted on the anterior surface of the uterus, this being accompanied by free hemorrhage. Furthermore, babies were injured by the too deep penetration of the knife in the uterine musculature.

Improvement in operating in general, as well as other factors, has shown that time is not the only element which enters into a successful operation. Due thought to the duration of anesthesia during a forceps delivery might have brought to mind that undue emphasis was placed on the necessity of shortening the time of anesthesia. Other conditions affecting the child's welfare during the performance of cesarean section are the administration of morphine too soon before starting the operation, thereby resulting in intrauterine asphyxia; trauma to the child by attempting delivery through an inadequately long incision; and disturbance in the child's nutrition in the presence of ablatio placentae and placenta previa. In recent times it has definitely been shown that prolonged anesthesia in the too slow extraction of the child is rarely a factor in the hands of competent operators.

*Second, The Welfare of the Mother.*—When it was realized that a living baby could be easily obtained, and that the earlier techniques often resulted in complications which were serious, if not fatal, to the mother, due consideration was given to her welfare.

The dangers or disabilities to which the mother is subjected when a child is delivered abdominally may be classified as immediate or late dangers.

## A. IMMEDIATE DANGERS

1. *Hemorrhage*.—From the earliest days of cesarean section, hemorrhage was one of the two most serious complications, the other being sepsis in the form of peritonitis. During the last twenty years hemorrhage has been so minimized, it is no longer the dreaded complication of former days. Improvement has come through the proper suturing of the uterine wound, the use of posterior pituitary extract injected intravenously if the condition so warranted, and the use of ergonovin, which will prolong the contraction of the uterus. Ether narcosis, which is responsible for relaxation of the uterus during operation, often has been supplanted by local infiltration anesthesia and by the various gaseous mixtures which have come into use during recent years. Blood transfusion, which was more of an innovation than the cesarean section itself twenty years ago, has been so simplified that it is now administered to the patient in her own bed, and, because of this, blood loss is easily replaced. The cervical or lower segment of the uterus when incised is much less likely to bleed than the corpus or upper segment. The performance of hysterectomy for uncontrollable hemorrhage following cesarean section has become a rarity at the present time.

2. *Trauma of Operation*.—Improved technique, gentle handling of the tissues, and conservation of blood have markedly decreased shock following abdominal delivery. It is conspicuously absent after the low or cervical cesarean section. It is more commonly observed in the cases of gravidoardiaces, but even in this group of cases it has been reduced to almost negligible proportions by operating under local infiltration anesthesia.

3. *Sepsis*.—Even more than hemorrhage, infection has been and still is the most important factor in mortality and morbidity in cesarean section. It stands out today as the most severe complication of the operation.

The contributing factors to infection in cesarean section are long labor, rupture of the membranes, repeated vaginal examinations, and the state of exhaustion and lowered resistance in which the mother has been placed after a protracted labor.

Protection against sepsis may be obtained by early interference when abdominal delivery is indicated and by the proper selection of the operative procedure. The work of Harris and Brown, carried out during the period of time in which we are reviewing the progress of cesarean section, has shown that bacterial invasion of the uterus occurred early in labor, even with unruptured membranes. The classical cesarean section offers no protection against peritoneal contamination at the time of intervention or thereafter. In view of the above cited work, this operation may be considered relatively safe before labor or at most at the onset of labor, but it becomes unsafe after labor has been established a number of hours, even though the membranes are still intact.

The low or cervical operations have considerably decreased the infections, although they have not absolutely controlled them. The progress of the last two decades has been in the saving of maternal lives

of those in whom abdominal delivery was imperative, by the application of the extraperitoneal technique and its modalities. Mayes, of Brooklyn, and Brown, of St. Louis, have shown by careful bacterial and clinical studies that infection at cesarean section could be decreased by the instillation of antiseptics in the vaginal tube before operation. The former advocated mercuriochrome and the latter neutral acriflavine. In a small number of cases of our own, we have found their contentions to be true. Thus, antisepsis has been added to asepsis.

#### B. LATE DANGERS OR DISABILITIES

1. *Invalidism*.—Following a major surgical operation, a number of women may have poor health for a more or less prolonged period of time. This is especially true if the operation has been associated with sepsis and hemorrhage. The period of recovery from operation varies with the patient's general condition at the time of intervention and with the presence or absence of postoperative complications.

2. *Sterility*.—In marked infection with suppuration following cesarean section, there may be partial or, in the severe cases, complete destruction of the endometrium, sometimes resulting in sterility. Two such patients have come to our observation. In one, there had been prolonged uterine suppuration following a peritoneal exclusion operation, and in the other, extreme sepsis following the Gottschalk-Portes exteriorization of the uterus. In both, the endometrium completely sloughed off, and these patients have never menstruated since. In the lesser degrees of sepsis, while amenorrhea may not result, there may be enough endometrial disturbance to cause sterility.

3. *Rupture of the Uterus*.—Imperfect healing of the uterine incision with subsequent rupture in following pregnancies and labors is to be thought of when cesarean section is contemplated. Statistics show this to occur in about 3 per cent of the classical cesarean section cases, and less than 1 per cent in the low or cervical operations. This is another respect in which the low operation has increased the safety of abdominal delivery.

The six factors mentioned above have been influential in the development of the technique and of the progress made in the performance of cesarean section in the last two decades.

#### PROGRESS IN TECHNIQUE

Before 1920, Beck, DeLee, Polak, and myself were strong advocates of the newer method of performing cesarean section. At that time the classical operation was the method universally used in America. During the twenty years which followed, the low or cervical cesarean section, to which DeLee has applied the term *Laparotrachelotomy*, has gradually supplanted the older operation in a number of important clinics, and DeLee, more than any other, must be given the credit of popularizing this intervention by his constant emphasis upon its superior merits. During the period of review, minor modifications in technique have been added by numerous operators. The important principles rest upon the fact

that in the performance of cesarean section the lower uterine segment may be approached in one of three ways: (1) intraperitoneally; (2) transperitoneally (peritoneal exclusion); and (3) extraperitoneally. In each instance the lower segment may be opened by a longitudinal or vertical incision, or by a transverse incision.

1. *Intraperitoneal Cervical Cesarean Section*.—This is referred to as the Kroenig-Beck-DeLee, and low flap operation. Essentially it consists of a vertical abdominal incision, a transverse incision in the visceral peritoneum, separation of the bladder with a lower flap of peritoneum, the dissection of an upper flap of peritoneum if one prefers, and a vertical incision in the lower segment. After delivery, the cervical incision is closed and the peritoneal flaps overlapped, sealing the uterine incision from the general peritoneal cavity.

In 1926 I proposed the transverse incision placed entirely in the lower segment after free separation of the bladder, with the main idea of preventing extension of the incision in the musculature of the uterine corpus when the lower segment was not well formed, or when delivering a large fetus. Munro Kerr had advocated a similar transverse incision which he placed at the isthmus or junction of the corpus and cervix without mobilizing the bladder.

2. *Transperitoneal Cervical Cesarean Section (Peritoneal Exclusion)*.—This operation is known as the Veit-Fromme-Hirst procedure. Veit and Fromme of Halle, in 1908, proposed a method whereby an extraperitoneal space for delivery was created by uniting the layers of the dissected visceral peritoneum to the parietal peritoneum by means of sutures or clamps, to protect the peritoneal cavity from the spill, and to leave the uterine incision outside of the general peritoneal cavity during the process of healing. Barton Cooke Hirst of Philadelphia, working independently, offered a similar procedure. More recently E. F. Smith of New York submitted a technique of peritoneal exclusion through a Pfannenstiel incision, and with a transverse incision in the lower segment in order to overcome one of the disadvantages of the Veit-Fromme-Hirst, namely the fixation of the lower uterine segment to the abdominal wall. Smith's operation is a modification of Sellheim's third method proposed in 1908. Peritoneal exclusion is recommended for the woman who has been long in labor, with or without ruptured membranes, but with potential infection. That the procedure recommended by Smith protects such a patient against peritonitis was forcibly brought to my attention in the case of a young woman on whom I performed this operation, after she had been in labor nearly forty-eight hours, and when she showed signs of exhaustion and early infection. She had a febrile puerperium and septic endometritis, her temperature reaching 105° F. for a number of days. She was discharged from the hospital at the end of two and one-half weeks, and examination two months later showed the uterus to be well involuted, in forward position, freely movable, and the pelvic organs in normal condition. Although she ran this septic course there were no signs of peritonitis.

3. *Extraperitoneal Cesarean Section*.—The extraperitoneal cesarean section is represented by the operation of Latzko. Advantage is taken

of the loosening and raising of the peritoneal sac from the lower uterine segment after a long labor. This procedure is performed through a vertical abdominal incision, the intact peritoneal sac is raised upward from the bladder and the bladder is displaced laterally to the right. This clears a space in the lower segment which is ample for the placing of a longitudinal or vertical incision of sufficient length for delivery. This method, reserved for potentially or frankly infected women, has replaced the radical or Porro cesarean section in a number of clinics. Its technique is more difficult than that of the intraperitoneal and transperitoneal operations, but in the hands of a trained pelvic surgeon, the difficulties are far from being insurmountable.

Edward G. Waters of Jersey City, New Jersey, during the present year, has published on the supravesical extraperitoneal cesarean section a true extraperitoneal operation simpler in performance than is the Latzko. In his method Waters has substituted a transverse incision for the longitudinal incision of the lower segment as used by Latzko. The operation of Waters will no doubt prove to be the most popular as it is taken up throughout the country.

*Vaginal cesarean section*, devised by Dührssen, for the rapid emptying of the uterus before term, and also to overcome the disadvantages of accouchement *forcé*, was used during the days when it was felt that the uterus should be emptied immediately for eclampsia. During the last twenty years the treatment of this disorder has been along conservative lines, treating the toxemia and disregarding the pregnancy for the time being. As a result of this the vaginal cesarean section has practically disappeared from the obstetricians' armamentarium.

Gottschalk-Portes operation, or temporary exteriorization of the uterus, has rendered important service in the exhausted, badly infected patient. Its employment will always be necessarily limited. I have saved two maternal lives and one fetal life by resorting to this procedure, when it was felt that all other methods would have failed.

#### COMMENT

A careful consideration of the progress of cesarean section from 1920 to 1940 has shown us that this operation is not a panacea for all obstetric ills. The indications, which doubtless were extended because of the increased safety of the low or cervical operations, should be carefully evaluated and should be reduced to a minimum. While the general surgeon, technically, may perform a perfectly adequate operation, his training is not such that he may evaluate the purely obstetric methods against abdominal delivery in a given case. In such instances, the requirement of a consultation with an obstetric consultant, as is done in a large number of hospitals, will have a salutary effect in reducing morbidity and mortality. The improved results of cesarean section in the hands of the trained obstetric specialist may not be due to the fact that he can perform the operation better than the general surgeon, but rather because of the fact that his obstetric training has taught him the contraindications to this operation, which he observes.

The chief contraindications to cesarean section are (1) a dead child, except in the presence of an absolute pelvic indication; (2) poor physical condition of the mother; (3) improper surroundings for aseptic technique; (4) a patient infected from protracted labor, vaginal examinations performed with questionable antisepsis and asepsis, and rupture of the membranes; (5) the classical cesarean section is absolutely contraindicated in the presence of a potential or frank infection.

The newer methods of performing cesarean section, largely standardized during the last two decades, will doubtless continue to play an important role in reducing morbidity and mortality. Finally, careful prenatal study, the use of x-ray pelvimetry, recently developed, examination before labor, under anesthesia if necessary, a test of labor under aseptic conditions, followed by the low or cervical operation when indicated, the use of vaginal antiseptics added to a rigid aseptic technique, and limiting the operation to strict indications will all help in keeping morbidity and mortality in cesarean section at the lowest possible figure.

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## TWENTY YEARS OF PROGRESS IN ENDOCRINE STUDIES OF REPRODUCTION

C. F. FLUHMAN, M.D., SAN FRANCISCO, CALIF.

**A**MONG the many achievements of medicine of the past two decades, the advances in our knowledge of the endocrine glands must rank as one of the brightest chapters. Of primary interest in this field have been the numerous studies dealing with reproduction, and they have led to discoveries which have clarified many phases of sexual physiology and pathology and also yielded active substances of inestimable value in the therapy of many obstetric and gynecologic diseases.

In the early twenties, a few pioneers struggled with various aspects of these problems, but the forties see a veritable army of investigators and the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* has become an important medium for reporting the results of their work. Evans and Cowles note that during the year 1939 a total of 2,807 papers of endocrine interest were published in 221 journals, and that 34 per cent of this number appeared in eight publications. It is noteworthy that the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* ranked sixth in this group, with a total of 66 contributions.

In the short space available for this review it is impossible to give a complete analysis of the progress made during the last twenty years in endocrine research dealing with reproduction. Nevertheless, on this anniversary of the *JOURNAL* it is of some interest to note a few of the fundamental discoveries which have been made during its lifetime.

### GONADOTROPIC HORMONES

On the basis of clinical observations and of early experiments on hypophysectomized dogs, the existence of a pituitary-gonadal interrelationship long has been recognized; but our present knowledge of the gonadotropic hormones may be said to have originated in 1921, when it was shown that clear-cut changes in the ovaries of rats follow the prolonged administration of suitable extracts of anterior lobe tissue. Since then corroboration has been advanced by many experiments with extracts or implants of fresh material in immature and mature hypophysectomized and intact animals.

As it does with so many other endocrine functions, the anterior lobe of the hypophysis controls the activities of the ovaries. It is responsible for the development of the primary follicles into mature Graafian follicles, ovulation, corpus luteum formation, and indirectly also for the production of ovarian hormones which in turn act on the accessory genital organs. These effects may be readily induced in immature or hypophysectomized rodents, but the question as to whether they are due to one or more hormones is not completely answered. There is strong evidence at present that two factors are concerned, one, a "follicle-stimulating" hormone, and second, a "luteinizing" hormone. It is

also claimed that there is a third, an "interstitial-cell-stimulating" hormone. The final answer to this problem awaits the chemical identification of the active pituitary substance or substances concerned with these changes.\*

With the exception of glands obtained from pregnant women, the anterior hypophyses of men and women, at all ages from fetal life to senility, have strong gonadotropic properties. In addition, anterior pituitary gonadotropin may be demonstrated in the blood and urine by means of the Aschheim-Zondek test under certain circumstances. For instance, its concentration increases at about the time of ovulation during the normal menstrual cycle, and large amounts are observed following castration or the menopause. These findings indicate that the ovaries also act on the anterior lobe and inhibit the production of its gonadotropin, a fact which is recognized in attempts to explain the mechanism of the menstrual cycle.

In 1928, it was announced that a potent gonadotropic substance occurs in the urine of pregnant women, and its demonstration is now widely employed as a "pregnancy test." At first it was believed that this hormone is produced by the anterior hypophysis, but evidence is accumulating showing that it is elaborated by the placenta. There are many biologic differences between the two gonadotropins. For instance, in hypophysectomized rats anterior lobe extracts stimulate the growth of follicles and the development of corpora lutea, while the injection of preparations of urine from pregnant women merely results in a hypertrophy and hyperplasia of the interstitial tissue. It also has been shown that a gonadotropin is formed in cultures of placental cells. The hormone found in pregnant women is now known as the "chorionic gonadotropic hormone"; but as in the case of the other gonadotropins, its chemical structure has not been determined. In addition to the placenta, it is also produced by cellular constituents of hydatidiform mole, chorioneopthelioma, and certain tumors of the testes.

Ten years ago another gonadotropic factor, having certain biologic properties common to both the anterior pituitary and chorionic hormones, was discovered in the blood of pregnant mares. This remarkable substance is exceedingly potent in stimulating the gonads of many species. It occurs in the blood of mares during the middle third of the period of gestation, and is excreted only in small amounts, if at all, in the urine. This equine hormone may in time become an important therapeutic agent.

#### LACTOGENIC HORMONE

Among the many functions attributed to the anterior hypophysis, the fact that it stimulates lactation is of special interest to obstetricians. Although many experiments with crude anterior lobe preparations resulted in changes in the mammary glands, now it is known that they are due, not to a general reaction involving many glands, but to prolactin, a specific product of the hypophysis. This substance, in ad-

\*Since this article was written the chemical purification of the "luteinizing" hormone from anterior lobe tissue has been announced. It is a protein and also is identical with the so-called "interstitial-cell-stimulating" hormone.

dition to stimulating lactation in mammals and crop-milk formation in pigeons, also can depress the activity of the gonads, and it is an important factor in the development of brooding and maternal instinct.

#### ESTROGENIC HORMONES

The word *estrogen* is used as a collective term for all substances which induce changes typical of the estrous period in the vagina, uterus, and mammary glands, and the female secondary sexual characters. The careful studies of the estrous cycle of the guinea pig, rat, and mouse, conducted between 1917 and 1922, led to the development of biologic tests for these substances and acted as a stimulus to the tremendous amount of work which has since been done on the subject.

The administration of estrogenic principles to both normal and spayed experimental animals leads primarily to a growth of the accessory genital organs. Although there are certain species differences, the main changes consist of an increase in the depth of the vaginal mucosa and its differentiation into a thick stratified squamous epithelium; the endometrium grows, presenting large numbers of mitotic figures; the uterus becomes distended by the accumulation of serous fluid; there is a pelvic hyperemia; the uterine muscle hypertrophies; the amplitude and rate of spontaneous rhythmic contractions of uterine and tubal musculature are increased; and the uterus is sensitized to the action of the posterior pituitary oxytocic hormone. In immature animals estrogen leads to the changes familiarly associated with puberty, such as establishment of the vaginal introitus, the development of the genital organs, and the manifestation of the secondary sexual characters. It is of importance, also, in the growth of the mammary glands, since it stimulates the development of the primary ducts and the epithelium covering the nipples.

In primates who menstruate, the estrogenic hormones control the development of the secondary sexual characters and the changes in the genital organs which characterize the preovulatory phase of the cycle. In both monkeys and women, they induce a growth of the endometrium, corresponding histologically with the stage of proliferation, cornification of the vaginal mucosa, hypertrophy of the uterine muscle, and development of the mammary duct system.

Several biologic tests for estrogenic hormones have been described, and they are based on the reparation of the postcastration atrophy of the accessory genital organs of small laboratory animals. By this means it has been demonstrated that estrogens are widely distributed in nature, not only in living but in inorganic matter. In mammals it is generally held that they are produced by the ovary, but there must also be an extragonadal source, possibly the adrenal gland, because they are found in the blood and urine of women after castration; and there is good reason to believe that the human placenta is concerned in their elaboration. They have been demonstrated in the liquor folliculi of normal Graafian follicles, some atretic follicles, and young corpora lutea. They are produced in very great quantities in women during gestation, and can be found readily in both maternal and fetal blood and urine, amniotic fluid and placenta. During the course of the

menstrual cycle, the concentration of estrogens in the blood and urine varies, a peak usually being found at about the time of ovulation.

A truly magnificent contribution to this field was the chemical isolation of many estrogenic substances, accomplished in an unbelievably short time by several groups of investigators, working in friendly rivalry and yet each adding invaluable assistance. The estrogens which occur naturally in the human being are sterols, and to this group also belong cholesterol, the bile acids, ergosterol, calciferol, and androgenic substances. Three important principles have been isolated from urine and ovarian tissue. The first one recognized was *estrone* and given the formula  $C_{18}H_{22}O_2$ . A second crystalline substance was then isolated, named *estriol*, with the formula  $C_{18}H_{24}O_3$ . Finally, *estradiol*,  $C_{18}H_{24}O_2$ , was extracted from ovarian tissue and recently also from urine. The fact that these compounds are very closely related chemically, and one may be converted into the other, may prove of vital importance in determining the mechanism concerned with the metabolic processes of the physiology of reproduction. An interesting new field of investigation is the quantitative interrelationship of these estrogens during normal gestation and in the course of certain toxemias of pregnancy.

Additional studies of the chemistry of estrogenic hormones have led to many discoveries, one of them being that these active substances may be prepared synthetically. This opens up a field of considerable importance, not only in the study of endocrine physiology, but also in a practical manner, since it will enable commercial concerns to manufacture reliable products for therapeutic usage at much less cost.

#### PROGESTERONE

In the early years of this century, a number of experimental studies led to the realization that the corpus luteum is a gland of internal secretion. There was much obscurity, however, regarding its exact function, and only in recent years has this been clarified. It is now known that, unlike the estrogens, the hormone of the yellow body is a specific substance produced by the ovary. An accurate biologic test for its demonstration has been developed, many aspects of its physiologic activity have been investigated, and it has been isolated as a pure chemical compound.

The hormone of the corpus luteum has been named *progesterone* and its effects, naturally, are apparent when this structure has reached a complete stage of development. The most striking are the pregestational changes which it induces. They are seen in the production of "pseudopregnancy" in certain mammals and the characteristic "post-ovulatory" or "secretory" stage of the endometrium of women and monkeys. Thus, it prepares and sensitizes the uterine mucosa for the nidation of the fertilized ovum. When the hormone is administered for a prolonged period, it prevents the onset of menstruation, and it also inhibits the normal rhythmic contractility of the myometrium.

Progesterone is chemically closely related to the estrogens and androgens, and has the formula  $C_{21}H_{30}O_2$ . It exists in two different

forms, the main difference between the two resting on a difference between their melting points. It also has been prepared synthetically.

A biologically inert substance, *pregnanediol*, with the molecular formula  $C_{21}H_{36}O_2$ , has been isolated from the urine of women in the post-ovulatory stage of the menstrual cycle and during pregnancy. It appears that this substance must be regarded as a metabolic end-product of progesterone and is excreted in the urine at a time when there is an active corpus luteum.

A more recent development of this work has been the synthetic preparation of *pregnenolone*, which is active orally, and induces physiologic effects comparable to those of progesterone.

#### ANDROGENIC HORMONES

A reference to the male sex hormones, the androgens, is necessary even in such a cursory review as this. These substances are sterols, closely related to the estrogens and progesterone, and they are found in the urine of women just as estrogens appear in appreciable amounts in the urine of men. The exact relationship between these various substances in normal physiologic processes still is not clear and must await further light.

The androgens have a definite masculinizing influence, acting directly on the accessory genital organs and influencing the development of the secondary sexual characters. From this viewpoint they may be regarded as the male equivalent of the estrogenic hormones.

Many substances have androgenic properties, but three are of importance because they occur naturally in the human being. Two, namely *androsterone* and *dehydroisoandrosterone*, have been obtained from urine, while *testosterone* originally was extracted from testicular tissue. The latter hormone has aroused considerable interest because of its employment with apparent success in the treatment of certain gynecologic and obstetric disorders.

#### THE MENSTRUAL CYCLE

The concepts of menstruation generally accepted in the early twenties were based altogether on the previous histologic studies of the German school. These had demonstrated the existence of an anatomic ovario-uterine cycle, and today they are still acceptable, although some of the original physiologic interpretations have been disproved. For instance, it was maintained that menstruation could not occur without a preceding ovulation, and that the ovum was the guiding factor determining when the menses appear.

A great impetus to the study of the menstrual cycle came with the adoption of monkeys as suitable laboratory animals. On the basis of many extensive investigations, conducted mostly in this country, it is now realized that menstruation in the *Macacus rhesus* is practically identical with this process in women. If findings in monkeys are not necessarily applicable to the human being, they at least pave the way for more discriminatory studies. The fact that the ovum exerts no control was clearly shown by a series of brilliant experiments in which

eggs were washed out of the Fallopian tubes immediately after ovulation, and there was no resultant interference with the succeeding menses. The demonstration of "anovulatory menstruation," in both monkeys and women, has made the dictum "Ohne Ovulation, keine Menstruation" retire to oblivion.

The role of the various hormones in the menstrual cycle is much better understood, and actual menstruation has been reproduced in spayed monkeys. It is known that the anterior hypophysis controls the function of the ovaries, the estrogens bring about the proliferative growth of the endometrium, and progesterone induces the premenstrual qualitative changes necessary for the successful implantation of a fertilized ovum. Although there is no lack of theories, mostly based on the interplay of ovarian and anterior lobe hormones, a completely satisfactory explanation for menstruation itself is still lacking. There is good reason to believe, however, that the flow is initiated, not by some positive factor acting on the uterine mucosa, but from the cessation of ovarian hormone influence. A step forward in our understanding of the mechanism actually concerned with the desquamation of the endometrium has been the study of this process in implants in the anterior chamber of monkeys' eyes and the discovery of the important part played by the fine blood vessels.

Superstitions die hard, and today many still believe that women menstruate regularly at twenty-eight-day intervals, and that estrus and menstruation are comparable phenomena. Nevertheless, ample evidence has been adduced, showing that estrus in the lower animals occurs at the time of ovulation and not at a period corresponding to that of the menses. Also, many reliable records of the length of the menstrual cycle have been published in many countries supporting the oft-quoted statement that "the only *regular* feature of menstruation is its *irregularity*."

The last two decades have seen great advances in our knowledge of the physiology of reproduction. Much remains to be done, and the work continues. It is enhanced by the development of methods of study such as biologic and chemical tests for the various sex hormones, the careful utilization of menstrual calendars, the determination of the pH of the vagina, the interpretation of vaginal smears, the histologic examination of biopsy specimens of the endometrium. These procedures are not necessarily of any value in clinical work but they are additional "tools" for investigating normal physiologic processes which must be understood before a successful approach can be made in dealing with pathologic conditions. It would not be surprising if in the next forty volumes the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY should record even much greater progress than it has in the past twenty years.

## THE ENDOCRINE THERAPY OF FUNCTIONAL OVARIAN FAILURE

E. C. HAMBLEN, M.D., DURHAM, N. C.

**G**YNECOLOGISTS relate, either by fact or by theory, many aberrations of gynecic function to ovarian failure. A great bulk of all organotherapy has been directed toward the correction of these functional disturbances of women. Enthusiastic adventures in therapy have overshadowed frequently basic failures to evaluate critically the underlying functional pathology.

The sequelae of ovarian failure vary in gravity with the time of occurrence of the failure (i.e., during adolescence, sexual maturity, and the climacteric) and with the degree of its completeness. The etiologic primacy of hypoovarian states is varied: The cause may be intrinsic to the ovaries or the ovarioendometrial system; it may be due to functional alterations in glands other than the ovaries; it may be wholly nonendoerine, as for instance, that failure precipitated by constitutional diseases, nutritional states, or local pelvic factors. Measures designed to overcome ovarian hypofunction are diverse; if these are employed rationally, they should be based upon secure diagnostic data. The ultimate choice of therapy is influenced frequently by the marital status and maternal aspirations of the patient. Except in instances of patients whose ovarian failure is due to the climacteric or to surgical or roentgenologic menopause, or under circumstances wherein the lowered fertility attendant upon the ovarian failure is not undesired by the patient, the true criterion of successful therapy is its ability to institute or restore cyclic ovarioendometrial responses compatible with the fertile state.

A critical analysis of the various therapeutic regimes yields a paucity of data regarding the modus operandi of individual agents and supplies little unequivocal proof that complete physiologic salvage is effected. A brief survey will be made of some of the endocrine agents commonly employed in the treatment of ovarian failure.

*Thyroid Substance.*—Powdered thyroid gland continues to hold a pre-eminent place in gynecic therapy. Many recent authors advise its use in the treatment of habitual abortion, endocrine sterility, and all of the various irregularities of bleeding. Most reports emphasize the high incidence of pregnancies in women with hypothyroidism or with presumed endocrine sterility following thyroid therapy, or describe the regulatory effects of this therapy upon azygous bleeding.

In reality, thyroid substance, the earliest known active endocrine agent, has received less critical study of its gynecologic roles than any of the various gonadotropins or sex sterols isolated during the past fifteen years. Clinical and experimental data on thyro-ovarian interrelationships have suggested many conflicting theories. Perhaps, the most generally accepted one of these assumes that ovarian levels of

function fluctuate with alterations in the general metabolism of oxygen. I have been unable to find any critical studies of endometrial responses to thyroid therapy or any studies of ovarian levels prior to, during, and following this form of therapy. I have not observed, personally, a single instance in which intensive thyroid therapy of patients whose bleeding occurred from estrogenic endometria was followed by bleeding from progestational endometria, i.e., no proof that ovulation was induced, even in patients who presented typical signs of myxedema. Regulation of the frequency and duration of bleeding has been observed to occur independently of a qualitative change in ovarian function; this observation is compatible with a concept of a simple speeding up of metabolism. I have observed pregnancies after thyroid therapy in women, whose endometriotropic and hormonal studies indicated no ovarian failure. These occurrences have been related to the ability of thyroid substance to overcome existing gametopathic factors due to inefficient local metabolism of oxygen in the ovaries.

*Chorionic Gonadotropins.*—The first gonadotropins available, those prepared from pregnancy urine or placenta, despite early enthusiastic reports, have been shown incapable of inducing ovulation in ovaries not spontaneously exhibiting normal cycles. Augmentation of normal responses, as judged by the occurrence of multiple corpora lutea or by amplification of the progestational phase, may be produced by therapy with these agents. Any regulatory effects exerted upon the character of estrogenic bleeding are relatable to alterations induced in estrogenic metabolism, chiefly that of increased destruction or elimination of those substances.

*Pituitary Gonadotropins.*—These appear, on the basis of all animal studies, to be the logical therapeutic substances when ovarian failure results from hypopituitarism. Experience with the commercial preparations of these has been generally disappointing. All of these preparations admittedly are too low in unitage of active principles to warrant any significant therapeutic expectations. Most pharmaceutical organizations have reported little or no success in economical concentration of these extracts; other extrapituitary sources have been explored.

On several occasions I have secured definite gonadotropic responses to intensive therapy with an active pituitary powder, not available commercially, in patients with pituitary emaciation and cachexia (Simmonds' disease). These responses simulated those reported following similar therapy in the hypophysectomized female monkey; correction of genital regression, initiation of bleeding when uterine enlargement and endometrial proliferation permitted and eventually restitution of normal ovarioendometrial cycles, judged by the spontaneous occurrence of progestational bleeding.

*Equine Gonadotropins.*—My early experiences with gonadotropins derived from the serum of pregnant mares indicated that follicular maturation (i.e., estrogenic metabolism) was enhanced by their employment in some women with estrogenic bleeding. I failed to find any evidence that this stimulation proceeded to the point of producing ovulation. It was shown subsequently that several times the dosage required to produce follicular stimulation in the sexually mature

woman was unable to call forth any recognizable responses in the ovaries of climacteric women. I have reported that, whereas occasionally rapid and complete sexual maturation followed equine gonadotropin therapy in young women with classical hypoovarianism, the majority of these women failed to obtain any signs of ovarian stimulation. These studies, all of which formed the basis for a theory that only those ovaries, which were receptive and yet which were receiving inadequate intrinsic gonadotropic stimuli for full follicular responses (i.e., instances of ovarian failure due to hypopituitarism), were amenable to this form of therapy, were overshadowed to a great extent, by the therapeutic enthusiasm aroused by reports that normal ovarian cycles could be augmented by injections of equine gonadotropins. Two important facts were overlooked in the haste of some clinicians to adopt this new therapeutic weapon: (1) Normal ovaries do not require therapy, whereas ovaries which have failed do not necessarily preserve the receptivity of normal ovaries; (2) no proof has been submitted that even when receptivity of ovaries to equine gonadotropins exists, full physiologic responses may be induced (i.e., ovulation and proliferation of the corpus luteum), except occasionally as a part of response of certain patients with classical adolescent hypoovarianism; in other words, equine gonadotropins, even under most favorable circumstances, may not do a full job of complementing pituitary deficits.

*Estrogens.*—The ability of these sterols to produce sexual maturation (i.e., enlargement of breasts and genitals, and epiphyseal union) in patients with classical adolescent hypoovarianism is well known. Since no stimulation of the gonads occurs, normal physiologic ovarian cycles are not initiated and salvage of the patient for procreative functions is not effected. The fact that estrogenic therapy stops excessive or prolonged estrogenic bleeding offers a simple method for hemostasis in some instances of menometrorrhagia due to ovarian failure.

The subjective symptomatology of the climacteric is treated commonly with ovarian principles, the rationale being that of supplementing for the physiologic hypoovarianism of this physiologic epoch. The use of gonadotropins at this time is irrational, since the endocrine basis of sexual regression is the development of an intrinsic ovarian refractivity to pituitary stimuli. The desideratum of estrogenic therapy for the relief of the crises of the vegetative nervous system at this time is to mollify symptoms but not to eradicate them. Overtreatment is common at this time and results in undesired sequelae: (1) the normal processes of sexual regression may be prolonged or even halted; (2) undesired irregularities of bleeding may be produced; (3) overstimulation of climacteric endometria may favor carcinogenesis. Small amounts of estrogens by mouth often suffice to secure grateful stabilization. Only a minority of women requires any endocrine therapy. Sedatives, reassurance, and correction of environmental and social conflicts often make endocrine therapy unnecessary.

*Progesterone.*—Progesterone is anti-estrogenic and increases the amount and duration of estrogenic bleeding by producing further critical falls in estrogenic levels. The concomitant administration of estrogens and progesterone is necessary to secure satisfactory proges-

tational responses in patients with spontaneous ovarian failure. The use of progesterone in anovulatory failure of the ovaries does not restore normal ovarian cycles; it may complement the endocrine deficit but does not circumvent the germinal failure.

*Stilbestrol.*—This is a synthetic drug, not a hormone. Its estrogenic properties, its high potency when given orally, its cheapness and its established toxicity render it, in my opinion, a dangerous drug to make available for general clinical use. It has no unique role in the treatment of ovarian failure; all its desired actions may be accomplished safely through the use of naturally occurring estrogens.

*Androgens.*—No clear-cut role in gynecic physiology or any rational therapeutic indications in endocrinopathic gynecology have been established for these sterols. Pre-existing ovarian failure is enhanced by androgenic therapy; all of the proved pharmacologic effects of androgens are "ovarian-negating" in nature.

*Cyclic Sterol Therapy.*—I have established the ability of cyclic sterol therapy (estrogens followed by estrogens and progesterone or estrogens and progesterone alone) to permit effective control of estrogenic menometrorrhagia; frequently this regulation continues after cessation of therapy. Ability to control excessive bleeding in the young woman by nonsurgical means, even though this effect may be only temporary, permits important applications: (1) Cyclic bleeding may be insured while anemia and other effects of hemorrhage are repaired; (2) the remission from excessive bleeding may permit adequate therapy of hypothyroidism or the medical treatment of pelvic congestion or infection; (3) this may permit tiding a young patient over a trying period of adolescence, until nature may complete the phase of sexual maturation, i.e., initiate fertile cycles.

I have suggested that this form of therapy might yield complete therapeutic salvage despite the fact that first impressions suggest for it only a temporizing or symptomatic role. The theoretical assumptions were advanced that ovarian conditioning might be effected by means of alterations induced in the pituitary function by cyclic sterol therapy or that disturbed metabolism and utilization of sterols by the endometrium might be corrected by this type of therapy and, thereby, overcome the disturbed ovarioendometrial responses characteristic of certain types of ovarian failure. Certain observations, which I have made, suggested the likelihood that a possible endometriopathic type of ovarian failure exists: (1) Some patients excrete cyclicly moderate amounts of pregnanediol (metabolic product of progestin), and yet bleed from estrogenic endometria; (2) many patients with functional estrogenic bleeding give minimal or no progestational responses despite repeated cycles of sterol therapy; (3) patients with adolescent hypovarianism who have failed to respond to equine gonadotropins may respond following intensive estrogenic therapy which has produced significant uterine hyperplasia and endometrial proliferation.

Recently my associates and I have submitted evidence that complete physiologic salvage may be effected by cyclic sterol therapy in certain patients with ovarian failure. The post-treatment endometriotropic responses of 21 of a group of 51 young patients who received a total

of 217 cycles of sterol therapy for estrogenic bleeding, indicated that 9 of these continued to bleed cyclically from progestational endometria (a salvage of 42.85 per cent). Two of these 21 patients subsequently became pregnant; both had remained sterile previously during their period of marriage. (None of the patients treated had clinical hypothyroidism or physical signs of any endocrinopathy.)

*Cyclic Gonadotropic Therapy.*—In view of the fact that complete ovarian responses were not secured in ovarian failure (except occasionally in the adolescent type) from equine gonadotropins, I devised a system of cyclic gonadotropic therapy, based on the one-two, administration of equine and chorionic gonadotropins. It was hoped that this combined therapy might complement any existing pituitary deficits. The hemorrhagic-hemostatic responses to this therapy are not nearly as striking as those of cyclic sterol therapy. Regulation of the cycle by cyclic sterols or curettage is necessary frequently as a preliminary step to gonadotropic therapy when cyclic menorrhagia was to be treated.

The ultimate responses following completion of this therapy of a group of 10 young women who had had estrogenic bleeding can be reported at this time. Seven of these 10 patients continued to bleed rather cyclically from progestational endometria, while another became pregnant during the first series of therapy. (This latter patient, observed for two years previously, bled habitually from estrogenic endometria and during 4 complete pretreatment cycles excreted no pregnanediol.) The physiologic salvage of this group, accordingly, was equivalent to 80 per cent. (None of the patients treated had clinical hypothyroidism or physical signs of any endocrinopathy.)

Proof that cyclic sterol therapy and cyclic gonadotropic therapy salvage different groups of patients is afforded by these observations; one of the above 10 patients, not salvaged by gonadotropic therapy, had responded previously to sterol therapy; two of the above patients, salvaged by gonadotropic therapy, had failed to respond to sterol therapy; one of the patients failed to respond to either sterol or gonadotropic therapy.

*Other Therapeutic Measures.*—Other measures which may correct diverse grades and types of ovarian failure include: The surgical or medical treatment of hyperthyroidism; adequate treatment of diabetes mellitus with insulin; surgical handling of virilizing tumors of the adrenal cortex or ovary; roentgenotherapy of basophilic adenoma or hyperplasia of the pituitary; the adequate treatment of any disease or nutritional error which undermines the general health; the gynecologic handling of pelvic infection, congestion, or other conditions which impair the ovarian circulation. Despite old and new reports on the subject, I cannot subscribe to the belief that ovarian failure can be corrected by roentgenotherapy of the ovaries. The end results of such therapy, I believe, are more marked grades of ovarian failure.

#### SUMMARY

1. A large group of women with varying grades of spontaneous ovarian failure, with the exception of those of climacteric ages, may be sal-

vaged for the reproductive function by judiciously chosen and rationally administered organotherapy.

2. Thyroid substance is most effective in patients with hypometabolism, with or without associated signs of clinical hypothyroidism. Its primary effect likely is on the germinal apparatus. Little evidence exists that marked endocrine failure of the ovaries can be overcome by thyroid substance alone.

3. The cyclic use of the ovarian sterols results in the initiation or restitution of normal ovarioendometrial responses in a certain group of patients. The ovarian failure of this group of patients has been assumed to be related to an endometriopathic factor associated with disturbances in sterol metabolism.

4. The combined and cyclic employment of equine and chorionic gonadotropins permits physiologic salvage of another group of patients, whose ovarian failure is related to hypogonadotropic activity of the pituitary.

5. Other patients, especially those whose ovarian failure is related to incomplete puerperal recovery or to the climacteric, cannot be salvaged by any of these methods of organotherapy.

6. At present no clear-cut diagnostic criteria have been established for selecting appropriate groups of patients for cyclic sterol or cyclic gonadotropic therapy. Ovarian responses of these patients, therefore, must be evaluated by therapeutic trials of these methods.

7. Substitutional therapy with estrogens, roentgenotherapy for excessive estrogenic bleeding or other gynecologic measures, may be more applicable to an individual patient if maternal aspirations do not render necessary an attempt to salvage the patient for reproductive functions.

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## MODERN TRENDS IN THE ARTIFICIAL TERMINATION OF PREGNANCY AND LABOR

FREDERICK C. IRVING, M.D., F.A.C.S., BOSTON, MASS.

AT THE beginning of a note appended to *The London Practice of Midwifery*,<sup>1</sup> published in 1826, the editor of the American edition says in his introduction:

"The facts presented in the following tabular views, may be useful as having a tendency to increase the confidence of the young practitioner in the ample resources of nature, and may render him less disposed to have recourse to instruments and artificial assistance, a fault, however, not confined to the junior members of the profession."

In Table I are abstracted from this source data which represented the hazards of pregnancy and childbirth over a century ago, long before the days of antisepsis and asepsis, when doctors washed their hands after making vaginal examinations or conducting deliveries, but not before. Twenty years were to elapse before the discovery of general anesthesia; the clinical thermometer, urinalysis, the sphygmomanometer, pelvic mensuration, and prenatal care were far in the future. The second part of the same table shows the recent maternal mortality rates of three large American cities, which in two instances are the same as those from which were derived the death rates of a hundred years ago. While it is freely admitted that the vital statistics of those days may not be entirely accurate because of the difficulty which may have existed then in collecting such information, what amazes us is that modern results in obstetrics are not incomparably better. Undoubtedly certain changes in economic, social, and racial factors have played their part, but careful investigation

TABLE I

| DATE      |  | MATERNAL MORTALITY<br>PER 1,000 BIRTHS*        |
|-----------|--|--|
| 1781      | Westminster General Dispensary (London)                | 3.6  |
| 1808-1815 | Private Practice (Merriman's Synopsis)                 | 5.2  |
| 1814-1820 | Philadelphia, Bills of Mortality                       | 4.5  |
|           | New York City, Report of City Inspector                | 6.8  |
|           | Private practice of Dr. David R. Arnell, Goshen, N. Y. | 3.3  |
|           | Average  | 4.7  |
|           |  | MATERNAL MORTALITY<br>PER 1,000 LIVE<br>BIRTHS |
| 1930-1932 | New York   | 5.8  |
| 1931-1933 | Philadelphia   | 7.4  |
| 1933-1935 | Boston   | 6.8  |
|           | Average  | 6.7  |

\*Because of the lack of data it is impossible to determine the number of live births. From the statistical point of view such a correction would modify the figures very little.

of each death in these three cities by committees appointed for the purpose shows, in a disquieting number of instances, that most of the catastrophes have resulted from interference with "the ample resources of nature" in the processes of pregnancy and parturition. Among such abuses are the indiscriminate resort to cesarean section and, in many cases, the unjustified employment of pelvic operative delivery. While these investigations indicate no ill results in the routine induction of labor which is being practiced by some obstetricians, usually by artificial rupture of the membranes presumably at or near full term, this procedure is sufficiently radical to warrant some comment.

#### CESAREAN SECTION

In 1937 and 1938, 4,298 cesarean sections were performed in Massachusetts.<sup>3, 4</sup> During this time there were 128,100 births, which indicates that the doctors of this state believed it necessary once in every 29 pregnancies to perform a serious abdominal operation to complete the process of reproduction. It is extremely unlikely that the structural fabric of the women living in this commonwealth has changed much, except greatly for the better, from that of 100 years ago, when cesarean sections were performed only in the rarest instances as a last resort. Behind the appalling frequency of this operation lies the fear of the doctor, insufficiently skilled in the art of pelvic delivery and thus without the confidence that such skill affords, that in no other way when even minor complications arise can he be sure of securing living infants for his patients. If almost every cesarean section guaranteed that the baby would be born alive, such a belief might have some basis in reality, but such is not the case. Four thousand, two hundred and ninety-eight cesarean sections produced 379 dead babies; an infantile death rate of 8.8 per cent, which agrees closely with a rate of 8.5 per cent derived from a study of 3,037 cesarean sections reported by 11 American authors and collected in 1937.<sup>5</sup> When cesarean section is performed for the sole purpose of obtaining a living infant, it does not compete with normal delivery and low forceps, for in 12,371 delivered thus through the pelvis in our clinic the total fetal mortality, including stillbirths and neonatal deaths, was only 3.4 per cent.

No one will quarrel with the necessity for cesarean section in cases of actual cephalopelvic disproportion. There are also occasional instances of true uterine inertia, which, resisting attempts at stimulation, make abdominal delivery much safer than violent extraction through an incompletely dilated cervix. Cesarean section is indicated in complete and partial placenta previa when the child is alive, undeformed and almost at term, but not otherwise, as a competent obstetrician may achieve delivery by Braxton Hicks' version or the use of the Voorhees' bag with equal safety to the mother. Recent opinion indicates that cesarean section in cases of complete ablatio placentae results in a much higher mortality than does the conservative method which embraces rupture of the membranes, a pack, and a tight abdominal binder. It is not

the treatment for pre-eclampsia, eclampsia, nephritis, heart disease, tuberculosis, nor, we believe, for diabetes.

One thousand two hundred and eleven, or almost a third of these cesarean sections, were performed because of the same operation in the previous pregnancy. From 1929 to 1938 inclusive at the Boston Lying-in Hospital, 55 patients who had had previous cesarean sections were delivered 73 times subsequently through the pelvis. One patient was thus delivered 5 times, 3 thrice, and 9 twice. In no instance did the uterus rupture. One mother died of pulmonary embolism on the third post-partum day, an accident which might with equal possibility have occurred had a cesarean section been performed upon her. The maternal mortality rate, therefore, was 1.4 per cent. Four infants, or 5.5 per cent, were lost; 3 were still-born following premature separation of the placenta, and one had a spina bifida and meningocele. There were 13 deaths among the 1,211 patients, who in Massachusetts during 1937 and 1938 were subjected to repeated cesarean section, a mortality of 1.1 per cent. Although this is a low mortality rate, it is not substantially better than we obtained in our patients subsequently delivered through the pelvis. It certainly does not justify a laparotomy in every case.

#### ROUTINE PELVIC OPERATIVE DELIVERY

The word "prophylactic" is loosely employed in the modern American obstetric vocabulary. According to the *Encyclopaedic Dictionary* it means "defending or protecting against disease." If in the minds of some obstetricians of today the normal delivery of a baby that presents by the vertex is a disease, then "prophylactic version" and "prophylactic forceps" are good usage, but not otherwise. The policy of routine internal podalic version, which startled the obstetric world about twenty years ago, has fortunately made but little lasting impression. Thrilled by the manual dexterity of the arch apostle of this maneuver, many pilgrims returned home hoping that having but touched his mantle, they might have acquired a measure of his uncanny skill. Before long a series of lacerations in the mothers and of intracranial hemorrhages and spinal paralyses in their babies brought disillusionment. It has never been clear why anyone should wish to convert a normal vertex presentation into an abnormal pelvic one, and then to proceed with immediate extraction. Indeed, one of the notable advances has been the increased frequency with which external cephalic version has been used to correct breech presentation. Internal podalic version has a distinct place in obstetrics, but like all other obstetric operations, only on definite indications. Chief among these are prolapse of the cord after full dilatation of the cervix. At the Boston Lying-in Hospital, it was employed in only 0.5 per cent of 20,364 deliveries.

The routine use of low forceps, also, is by no means necessary. If the patient appears to be delivering her baby normally, there seems to be no valid reason to prevent her. On the other hand, prolonged pres-

sure against an unyielding perineum in some cases will cause intracranial damage, a fact which was recognized by Goodall<sup>6</sup> in 1934. Studdiford and Salter<sup>7</sup> have noted the frequency with which premature infants suffer from this cause, and their advice to deliver them by low forceps after an episiotomy is sound obstetrics. In our clinic, the policy is to deliver patients by low forceps after the scalp is showing, (1) if the fetal heart rate shows significant variations or (2) if there has been no progress for two hours. The incidence of this operation varies from 25 to 30 per cent; the fetal mortality of viable infants delivered normally is 3.7 per cent and of those delivered by low forceps 2.6 per cent.

The characteristic haste of some American *accoucheurs* to terminate labor is shown not only by their frequent resort to cesarean section but also by the readiness with which they effect operative delivery through an undilated cervix. Such an ill-advised policy can only result in laceration of the cervix with deep vault tears, prolapse of the uterus with cystocele, dissolution of the perineum, and a number of dead babies. The cautious obstetrician, if he also practices gynecology, should find little opportunity to perform plastic operations upon his own patients. Barring cephalopelvic disproportion, patience and expectancy will usually result in full dilatation of the cervix with descent of the head. Should uterine inertia set in, and there be no abnormalities of the presentation or in the adaptation of the head to the pelvis, pituitary extract given sparingly in one-minim doses will usually produce the desired effect. To those who, having had little experience with this drug, inveigh against its use, in any case even in such small amounts, with the blindness of religious zealots, we submit that we have so used it in several thousand cases not only with no bad effects upon mother or child, but, on the other hand, with uniformly good results.

#### THE INDUCTION OF LABOR AT TERM

The induction of labor toward the end of pregnancy, when performed for a distinct indication, is a most valuable procedure, and in preeclampsia it is a salutary measure for both mother and infant. Of late years, however, "delivery by appointment," usually by rupture of the membranes, for the convenience of the patient, and of the doctor, has come into vogue with certain obstetricians. Short series of cases have been reported to prove that it causes no ill effects, but no control series of cases that have not been tampered with have been published with them. In medicine, when a new policy is advocated, it is not enough to show that the results so obtained are no worse; if the innovation is an improvement the effect should be better. In 1937 Plass and Seibert<sup>8</sup> reported routine rupture of the membranes in 681 cases, stating frankly that the indications were rarely medical, but that most patients were induced to shorten their ante-partum stay in the hospital. No mothers died, and there was no increase in fetal mortality or maternal morbidity. There were, however, 5 cases of prolapse of the cord,

which they admit is greater than the usual frequency. There is yet no evidence, when the cervix is effaced and there is some dilatation of the cervix and in the absence of cephalopelvic disproportion or of an abnormal presentation, that in the hands of a well-trained obstetrician such a procedure is often productive of harm. On the other hand, should prolapse of the cord occur, or puerperal infection set in, the attendant should be willing to accept the blame for an accident which probably would not have happened had he not interfered with a normal pregnancy.

The general practitioner, if not the obstetric specialist, may derive some comfort from the incontrovertible fact that childbirth, if left alone, is usually a normal process. In sixty years, 73,532 women have been delivered in the poorer districts of Boston by third- and fourth-year students of Harvard Medical School, with the loss of 82; a death rate of 1.1 per thousand. Up to the establishment of the Pregnancy Clinie in 1913 the rate was 1.6 per thousand; since then it has been 0.5 per thousand. During the last six years, 5,033 women have been delivered with no deaths. All abnormal cases are sent into the Hospital; no operations are performed on the District except low forceps and multiparous breech extractions. Possibly such results smack of midwifery rather than of obstetrics, but be that as it may, it is not likely that the results would have been as good if 1 in 29, or 2,604 women, had been subjected to cesarean section, if several thousands of others had been delivered by "prophylactic" version or forceps, or if the membranes had been ruptured indiscriminately simply because the patients appeared to be at term.

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## CHANGES IN THE TREND OF EMBRYOLOGIC RESEARCH

GEORGE L. STREETER, M.D., BALTIMORE, MD.

**I**N THIS anniversary number it is perhaps not too far afield to look back at embryology as one of the basic subjects from which obstetrics and gynecology were in part derived. These lusty descendants have long since justified their own and independent spheres of usefulness, but embryology is still an underlying subject, and during the period covered by this anniversary, important advances in embryologic concepts have taken place. It is the purpose of this brief paper to outline what appears to me as an improved trend in our understanding of the mechanisms of development.

When the publication committee of this JOURNAL and its board of editors were studying embryology as medical students, great emphasis was being laid on the teachings of comparative embryology. Balfour and the Cambridge School were expounding on the elaborations of the three-germ-layer theory with great clarity. The continental investigators, taking advantage of the serial section technique, were writing extensively on the detailed structure of all manner of embryos. These studies culminated in such publications as the Hertwig *Hand-book of Comparative Embryology* and the Kiebel *Normen Tafeln Series*. The burden of their writings was that there are morphologic ground plans in development and that these with various adaptations are followed in all animal forms. To them it was the pattern that was important, and this was of an ordained design. It was the concern of the investigator to discover this design, with the expectation that it would furnish the key to development. Thus the biogenetic law and the three-germ-layer theory were widely accepted with the reassuring belief that nature's processes are simple when one has discovered the basic morphologic plan.

While Europe was industriously inventing doctrines and at a time when some of their embryologic tenets appeared to be permanently established, a new direction of research sprang up; and this was largely due to workers on this side of the Atlantic. The details of development were dropped and interest was concentrated on end products. The attempt was made to discover the laws of breeding and cross-breeding, and the science of animal genetics therewith came into existence. The geneticist soon settled on the chromosomes as the responsible agents for the end products and an American school, using the rapid breeding fruit-fly, the *Drosophila melanogaster*, as the test animal, accumulated a great body of observations and deductions by which the end products of development could be predicted and controlled to a remarkable extent. There was, however, no thought in this of upsetting in any way the prevalent embryologic teaching of ground plans and germ layers. These investigators were not concerned with the visible phenomena of development and were not actually handling embryonic tissues.

In the meantime interest had arisen in two other directions which did involve handling embryonic tissues. One of these is represented

by a group who by means of cultures in artificial media, were able to isolate individual embryonic cell masses and study their characteristics in the living state. In this way, much has been learned regarding the requirements for the survival, growth, and differentiation of embryonic tissues. The important fact was revealed that differentiation requires a sufficient mass of tissue. This signified that cells are dependent on the influence of neighboring cells and particularly on those differing from them in certain potentialities. It was also found that in tissue cultures embryonic cells possess an unexpectedly large capacity for change in form. A given tissue having the form of a delicate reticulum, such as commonly seen in embryonic connective tissue, may, with a slight variation in the conditions, take the form of a mesothelium. The student of living cells has learned to distinguish the different types by their range of transformations instead of by any permanent characteristic form. It is form-behavior rather than a fixed morphology that must be relied upon.

The other group studying embryonic tissues comprises those who, using live embryos, have removed or transplanted larger or smaller parts at various stages of development and in this way have answered questions of regeneration, the specificity of tissues and the form and orientation of individual organs and parts. This led to the discoveries of the influence of different embryonic tissues upon each other and the dominance of some over others. By appropriate stimulation, duplicate organs could be "induced." It was further found that induction of new organs did not require living inductors, but the derived chemicals were similarly effective. Also to be mentioned is the large body of observations that has been made on the hormonal factors which serve as regulators of growth and development. These appear to be in the nature of environmental influences and therefore are to be grouped with the inductor agents.

As these discoveries became available to the embryologist, he has found that a more satisfactory analysis of development can be made than the classic one of the past which was based almost entirely on an artificial morphologic ground plan. The embryo, with the opportunities now existing, can be studied as a functional organism and the activities of its constituent cells can in large part be determined. It is found that these vary with the change in complexity and with the consequent change in physiologic requirements from stage to stage. The number of layers and the form of the cavities appear to be merely incidental and what were thought to be vestiges of phylogenetic importance are now in many instances found to be temporary embryonic structures, essential to a particular period of development. The present trend in embryology is thus to regard all parts of the embryo and its auxiliary tissues as having functions to perform. The investigator endeavors to distinguish which of these functions are for the immediate maintenance of the organism and which produce actual developmental alterations. It is now realized that the embryo at all stages is a living individual, and is to be explained as a biologic problem, rather than an exercise in purely morphologic abstractions. One now begrudges the immense amount of effort that has in the past been expended on discriminating between the ectoderm, mesoderm, and endoderm cells.

## UTEROTUBAL INSUFFLATION AS A TEST FOR TUBAL PATENCY, 1920-1940

I. C. RUBIN, M.D., NEW YORK, N. Y.

**U**TEROTUBAL insufflation was devised in 1919 as a nonsurgical method of determining tubal patency or nonpatency in cases of sterility. It developed indirectly from previous attempts to accomplish nonoperative exploration by the injection of fluids opaque to the x-rays. Prior to 1919, collargol (Cary, Dimier, Rubin) and the halogen salts (Rubin) were used to visualize radiooscopically the uterine cavity and lumen of the Fallopian tubes. These radiopaque substances had inherent disadvantages, notably chemical irritation, intratubal inspissation, and limited radiopacity in the strengths then employed.

The departure from the use of x-ray opaque substances and their substitution by oxygen was made to avoid undesirable results. Oxygen had already been introduced into the abdominal cavity by direct puncture and appeared to be well tolerated (Stein and Stewart). The insufflation of oxygen into the uterus and through the tubes was first carried out clinically in November, 1919. Certain symptoms, chiefly shoulder pains and epigastric distress which followed the insufflation, were relieved by reducing the amount of oxygen and by placing the patient in the knee-chest or Trendelenburg posture. Furthermore, from the outset some mechanical control over the pressure attending the insufflation was provided.

The indications and contraindications for the use of the new method were carefully considered. It was obvious that for clinical application every safeguard should be taken. Accordingly the volume insufflated was reduced to a necessary minimum, 50 to 150 c.c.; a siphon volumometer was added to the insufflation apparatus which already had included a manometer and a suitable uterine cannula. Vaginal and cervical hygiene, preference of the postmenstrual phase as the time of choice for performing the test, were further favorable steps.

Carbon dioxide was next substituted for oxygen, as the latter was found to cause somewhat persistent shoulder symptoms, lasting in many cases for twenty-four to forty-eight hours, unless a very minimal amount had been used (50 to 75 c.c.).  $\text{CO}_2$  has the great advantage over  $\text{O}_2$  in being more soluble and more rapidly absorbed. Furthermore the use of  $\text{CO}_2$  appeared to eliminate the possibility of embolism. Thus insufflation of an amount of  $\text{CO}_2$  equal to that of  $\text{O}_2$  was found to be resorbed in a few minutes, the patient being kept in the Trendelenburg posture.

It was early recognized that a constant flow rate was useful. Accordingly, the amount of gas to be introduced was estimated by the number of seconds required to reach 100 mm. Hg (15 seconds to 100 mm. Hg). This pressure rate flow was reduced to thirty seconds to 100 mm. Hg and later on to slower rates. In the last ten years approximately, I have endeavored to use the more convenient constant flow rate of 60 c.e. per

minute, which insures against undue reactions on the part of the uterine muscle and serves for comparison in the event the test is repeated for diagnostic or therapeutic purposes.

The addition of a kymograph in 1925, in which was incorporated a blow-off device for safety, enabled us to derive information that had previously escaped us. It not only provided a means of recording the graph of the insufflation (tubograph), but the pattern soon became recognizable as indicating normal physiologic function and abnormal deviations produced by underlying pathologic condition of the tubes. Thus rhythmic contractions associating normal tubal patency were differentiated from irregular, atypical contractions which characterized pathologic tubes. These atypical contractions varied both in depth of their force measured in terms of mm. Hg and in relation to their frequency and rhythmicity.

It was early observed that the pressure recorded in the case of closed tubes reached the maximum limit of 200 mm. Hg. In many instances the pressure after reaching a high level tended to drop spontaneously, which indicated a slight degree of patency. Kymographic insufflation enabled us to differentiate completely nonpatent tubes from partially patent tubes by the graphic patterns that were recorded. It moreover indicated to what extent a therapeutic mechanical effect upon the tubal obstruction was obtained and helped to distinguish uterotubal spasm from nonpatency. The kymographic insufflation apparatus has been modified since 1939 in only one respect, namely, in substituting a flow meter (Foregger type) for the siphon meter as originally employed.

The records obtained by kymographic tubal insufflation were checked at first by laparotomy observations in a series of cases and then by lipiodol injection. In practically all instances the findings were corroborated. In contrast to radiopaque substances the tubographs, properly interpreted, have the unique advantage of demonstrating in a few minutes, normal physiologic tubal function and deviations in function which are not possible by the former media.

A further step in the elucidation of the correlation between the tubograph on the one hand, tubal strictures and peritubal adhesions on the other, was to subject the dead and living organs to experimental reproduction of these conditions as far as it was possible. The dead organs were found to exert no action upon the gas which percolated through them, whereas the surviving extirpated organs demonstrated either normal rhythmic contractions under physiologic conditions and abnormal deviations under pathologic circumstances which were artificially reproduced.

It is of interest to note that rhythmic contractions are rarely observed with the naked eye during laparotomy and under anesthesia. This holds true in rabbits also, when the abdominal viscera are exposed although the intestines retain their peristaltic activity. However, when an abdominal window is sewed in, the oviducts are seen to exhibit vermicular movements.

The further development of kymographic tubal insufflation was in the field of biodynamic assay of hormones as well as oxytocic pharmacologic substances. It had been seen that the variation in tubographs at certain

phases of the menstrual ovulation cycle grouped themselves into certain patterns, while at the same time the force of the contractions could be measured in terms of mm. Hg. Experimental application of this method in the monkey in 1936, and thereafter in the rabbit, paved the way for its clinical application as a biodynamic assay of hormonal therapy. It was reserved chiefly for cases of prolonged amenorrhea and certain cases of menopause. Other substances, such as pituitrin, pitressin, pitocin, thymophysin, adrenalin, and acetylcholin, were also checked as to their pharmacodynamic action by intravenous injection in the rabbit.

In the development of the method of uterotubal insufflation during the past twenty years, a period covering the progress of this JOURNAL, many notable contributions were made by others. The limitations of space allotted to this article make it impossible to enumerate all of them.\* In this brief review, however, one cannot fail to mention a few of the pioneers.

Among the first to adopt the new method were Reuben Peterson, 1921, 1922 and 1928; Dawson Furniss, 1921; John G. Clark, 1922; Robert L. Dickinson, 1922; R. S. Cron, 1922; H. Guthmann, 1922; J. J. Mundell, 1922; J. Novak, 1922; A. J. Rongy and S. S. Rosenfeld, 1922; E. Graff, 1923; S. R. Meaker, 1924. George Gray Ward established the first clinic for the specific use of tubal insufflation in sterility at the Woman's Hospital. Guthmann was the first to recognize the difference between the manifestations of pressure oscillations when the tubes were open and their absence when the tubes were closed. Henderson and Amos were the first to publish (1924) their observations on auscultatory findings during tubal insufflation, describing the tubal souffle in patent tubes.

Many modifications of the apparatus, including a departure from the use of oxygen and carbon dioxide by substituting air, and simple devices for injecting the latter soon appeared. Some of these changes were apparently instituted to suit the needs of various conditions peculiar to different countries. Many have sought to modify the uterine cannula by additional self-retaining devices, while others assembled different types of insufflation apparatus including several for kymographic insufflation.

The French group were among the first in recent years to appreciate the value of kymographic tubal insufflation in estimating the pharmacodynamic effects of oxytocics and hormones. Bonnet introduced a quantimetric flow meter for the  $\text{CO}_2$  and also devised a formula for calibrating the diameter of the stenosis in strictured Fallopian tubes.

Many comparisons between the value of lipiodol injection and tubal insufflation were made, while most numerous were reports on the diagnostic and therapeutic value of insufflation. A number reported upon the combination of insufflation with lipiodol injection, since Peterson and Cron employed transuterine insufflation for purposes of pneumoperitoneal diagnosis in gynecology.

\*Full acknowledgment will be included in a forthcoming volume on uterotubal insufflation.

Bacteriologic and pathologic studies were made by some authors in connection with the general scope of uterotubal insufflation and a few articles reported the results of insufflation in the presence of adnexitis. The interstitial portion of the Fallopian tubes claimed the attention of some authors, while several studied fetal tubes and those of the newborn by insufflation. A number of reports have dealt with air embolism and a few with fatalities following insufflation. Endometrial dislocation was discussed by an occasional author and one or two dealt with insufflation during menstruation, and indications and contraindications of the method were considered.

Work upon the physiology of the Fallopian tubes during the menstruation-ovulation cycle, with and without the method of uterotubal insufflation, was reported by several authors, while a few have specifically undertaken hormonal studies in the same connection. The combination of diathermy with tubal insufflation as nonoperative restoration of tubal patency and the use of hormones for the same purpose are to be found in several publications. Study of Head zones produced by distention with  $\text{CO}_2$  of ligated tubes and the nonsurgical reopening of ligated tubes by the same method are recent contributions. A few publications have dealt with its application in veterinary medicine.

The nomenclature of uterotubal insufflation has undergone considerable change, not only in its application in foreign lands but also in the English literature. Dawson Furniss made first reference to the Rubin test. Others have called it the Rubin method and transuterine insufflation test; while abroad many refer to it as perturbation, uterotubal persufflation, La Insuflacion tubaria, L'insufflation tubaire, Tubendurchblasung nach Rubin, and Kymographic insufflation.

The nonoperative method of determining patency of the Fallopian tubes appears to have stimulated renewed interest in the sterility problem as a whole, in the opinion of some authors, paving the way for more concentrated attention to the nonmechanical aspects.

As a result of cumulative experience with uterotubal insufflation during the past twenty years, we are now able to estimate the etiologic importance of tubal obstruction in sterility. Without going into the extensive literature on the subject, a general idea of its incidence may be obtained from an analysis of 593 replies to a questionnaire\* embracing 86,113 insufflation tests performed in various parts of this country and abroad. According to these statistical data, there were complete tubal obstruction in 30.88 per cent of the cases and partial tubal obstruction in 8.85 per cent. My own series of 5,269 insufflations, the majority of which were kymographic, showed an incidence of complete tubal obstruction in 32.4 per cent and of partial tubal obstruction in 33.1 per cent.

Considering the number of authors, the variety of insufflation apparatus and individual technique, the different gases employed and the natural differences in the particular groups of patients making up the various series, it is to be expected that there will be some percentile disparity in the statistical results. Whereas, these are strikingly close

\*The questionnaire was sent out in early 1939 and replies were received during 1939-1940.

in the case of nonpatent tubes; the disparity is considerable in the partially patent tube series. It is particularly in this condition where kymographic insufflation has significance.

The method of uterotubal insufflation has undergone gradual development from its incipiency in 1919 to its present status as a precise and safe clinical nonsurgical test for determining tubal patency.  $\text{CO}_2$ , adopted as the gas of choice, has proved its usefulness and superiority over the years. Strict regard for clinical indications and contraindications and attention to the rules of technique are essential safeguards. The information derived from kymographic insufflation goes beyond the mere fact of tubal patency, yielding physiologic data not otherwise obtainable. It affords graphic records but, unlike hysterosalpingography, no photographic films. With hysterosalpingography it shares the same limitation; namely, the necessity for correct interpretation which in the last analysis is an art acquired by ample critical experience. Without going into its comparative merits, it is fair to say that uterotubal insufflation in careful hands can be utilized without untoward immediate accidents or sequelae in all cases where it is properly indicated for diagnosis and therapy.

## THE DEVELOPMENT OF MATERNAL WELFARE ACTIVITIES

FRED L. ADAIR, M.D., CHICAGO, ILL.

THE origins of the interest in mothers and babies are locked in the unwritten records of man, and even the earliest written records only hint at the customs of early civilizations. Doubtless the instinctive behavior of males to protect their mates and of the females to save their young were manifest in primitive man. As the family and the tribe developed and as the beginnings of society were established, there were more organized efforts. There came to be patriarchal and matriarchal systems, and both male and female as well as other deities came to be worshiped. The nomadic tribes and peoples had different mores than those who became more settled and better organized socially and economically. It followed more or less naturally that mothers and babies could and would receive more attention and consideration in the matriarchal and the communal systems. No doubt the tribes which lived in the same area for any length of time were afflicted with various types of infection. Obviously puerperal fever might have been among those disorders.

The various disorders which affected diverse members of the tribe led to various superstitions and fears and naturally the diseases which afflicted mothers were among those which eventually led to certain mores and religious rites which were designed to counteract the evil spirits which were responsible for the calamity. It is probable that in the nomadic tribes much of the care was self-care with the assistance of the husband, mothers, or some member of the family. It is unlikely that the tribal movement could be arrested by the episode of childbirth. In the communal and settled tribes those women who had experienced motherhood assumed the duty of administering care to those of their sex who were novices. Gradually this type of service fell to the lot of the older women of the tribe. This doubtless was the foundation of midwifery.

When complications arose, the assistance of the priests and the medicine man was summoned, and by means of rituals and incantations the devils were driven away and the woman survived or in case of failure she died.

The fecundity of these early peoples was high and the death rate was enormous. Living was precarious and life was cheap. The struggle for existence was difficult and sentiment played little role, the survival of the individual was apparently of little importance to anyone except himself. It is, of course, well known that weaklings at both extremes of life were frequently sacrificed, as primitive living required the self-sufficiency of the individual. We also know that abortions were frequently produced by very crude and often violent methods.

From these relatively simple tribal organizations more complex social systems arose and successive civilizations have risen and fallen leaving little trace of the development of obstetrics which was essential be-

fore any rational plan of maternal welfare could arise. The art and science of obstetrics has a long, a varied, and a spasmodic history. Its early course revolves around the care of the mother, and her interests were paramount and the sacrifice of the infant was often necessary. Maternal care was almost completely individual in that the midwife or doctor looked after his patient, and there was little thought of organized effort to care for the mothers of a community. Lying-in institutions were established but they were hotbeds of infection until the etiology and prevention of puerperal sepsis was determined and put into practice.

In his lectures of about 1776, Thomas Young, of Edinburgh, stated that there were two viewpoints of midwifery; one, the restricted limiting the practice to the care of the woman in labor, the other broader view encompassed the care of the woman and a knowledge of the whole field of human reproduction. He established a small hospital and made provisions for the care of women in their homes. This was in connection with the course of instruction in midwifery at the University of Edinburgh. Thomas Young was a pioneer though his name is little known. One cannot think of Edinburgh in connection with maternal welfare without calling to mind the great Simpson who did so much by establishing anesthesia and analgesia in obstetric practice. Space does not permit the mention of his numerous contributions. Antenatal care cannot be mentioned without thought of Ballantyne, also of Edinburgh, whose monumental pioneer work in this field is classic.

It is not within the scope of this article to present factual material dealing with the advancing knowledge of obstetrics. One can only hint at the devastation of human lives marked by the mute protest of the tombstones of mothers and infants of successive generations. One of the greatest killers was infection, and it took decades of accumulated experience and scientific observation on the part of men like Young, White, Gordon, Leeuwenhoeck, Holmes, Semmelweiss, Lister, and Pasteur to lay the foundations of our present knowledge of infection and its prevention.

The motives back of maternal welfare are mixed, but the objectives are clear. They may be succinctly stated as the preservation of the health and lives of mothers and babies, to minimize suffering and to maintain and improve the human race. The motives may be humanitarian or necessitarian or sentimental or materialistic. No doubt the desire for children and the falling birth rate have been potent factors among civilized races. One may view it from the standpoint of the welfare of the individual mother as the physician views his patient or one may take a broad sociologic view which embraces all mothers and all babies. What actuated Rösslein in writing the *Rosengarten* is not known, but a little rhyme in the preface of Kuhn's reproduction of the edition of 1513 is suggestive:

"For pay, I trust that I may see  
That women safe and happy be,  
But if such pay I am not given,  
Then I must get my pay from heaven."

There is, so far as my knowledge of the literature reveals, no complete exposition of the fundamental principles of maternal welfare until the little known but comprehensively and beautifully written book of William Buchan was published in 1803. His work was designated for the intelligent lay reader and was entitled *Advice to Mothers*. He presents in a lucid style most of the basic ideas which are accepted today as the essentials of maternal welfare. Naturally one would not accept the methods and technique of his day as advisable today. A couple of quotations from his introduction are pertinent to this discussion. Speaking of mothers he writes, "The want of proper instruction at an early period of life betrays them into a variety of fatal mistakes respecting their own health as well as that of their children." With reference to a general plan to reach all mothers, especially those living in poverty, he states, "I do not know any manner in which humanity, charity, and patriotism can be more laudably exerted, or even a part of the public revenue more usefully employed than in enabling mothers to bring up a healthy and hardy race of men, fit to earn their livelihood by useful employments and to defend their country in the hour of danger."

Pinard stressed the importance of the obstetric examination of pregnant women, and certain institutions were established in France for their care. This was about the beginning of the present century. At this period Ballantyne was establishing prematernity wards for the antepartum care of women with complications, and he prophesied in an imaginary conversation that by 1940 the obstetricians would wonder why those of a generation before had spent so much time and thought about the few hours of labor and so little concerning the nine months of pregnancy. This has been realized in our country and even further advances have been made, as complete maternal care is now recognized not only as desirable but as essential for the future welfare of our nation. Present events intensify this feeling as the future of our civilization depends upon us, while forces beyond our control are wrecking the civilizations of Europe. We have extended our ideas of maternal welfare to include preconceptional care as shown by legal requirements for premarital examinations and for the inclusion of the father in the educational and welfare program. The family is the social unit, and the mother is becoming to be recognized as the keystone in the arch of family welfare.

One can briefly mention some of the important events in the development of maternal care from the early beginnings of prenatal work in Boston under the leadership of Mrs. Putnam, the establishment of the Society for the Study and Prevention of Infant Mortality out of which the Joint Committee on Maternal Welfare originated. From this committee, formed twenty years ago, has come national, state, and local leadership in developing programs to conserve health and lives of the mother, the fetus, and the newborn. Its members have done noteworthy work in supplying medical leadership all over the United States, have worked hard, cheerfully, and voluntarily on Hoover's White House

Conference on Child Health and Protection, on various advisory committees of the Children's Bureau and those of the Maternity and Infancy Divisions of the various states. They have expended much ability and energy in making the often unpleasant but essential scientific and educational studies of maternal, fetal, and neonatal deaths. The American Committee on Maternal Welfare has replaced the Joint Committee and continues medical and nursing leadership in the field of maternal care by such activities as the publication of small obstetric manuals, pamphlets, and a quarterly bulletin. It has also created and sponsored the educational feature movie, "The Birth of a Baby," and the First American Congress of Obstetrics and Gynecology.

Various local organizations such as the Losenstine Clinic, the Maternity Centers of New York and of Chicago, the Frontier Nursing Service, and many others have assumed national significance. The most comprehensive national program had its beginnings in the Sheppard-Towner Law which was attacked and finally failed to receive federal appropriations. Similar and even more far-reaching legislation has been incorporated in Section V of the Social Security Act which has stimulated and put into effect educational, service, and research activities in the fields of maternal and infant health in various states and territories. All of these factors and many others have been responsible for the gratifying reduction in maternal mortality rates. There is more to be accomplished and morbidity as well as mortality must be considered. The stillbirth and neonatal death rates must be reduced and morbidity must be prevented.

Medical and nursing service, education, and investigation are vital, and programs must be developed locally to meet community needs. The basic principles are general, but their application must be developed and made by methods which are best adapted to the various localities.

The mania for war should not lead us to a neglect of the vital defenses of the mothers, the home, and the motherland.

## THE UNMARRIED MOTHER AS A MEDICAL AND SOCIAL PROBLEM

W. C. DANFORTH, M.D., F.A.C.S., EVANSTON, ILL.

THE mode of dealing with the unmarried mother and her child has come down from The English Poor Law and the English Property Law. In earlier days the bearing of an infant outside of wedlock was not considered an offense against the criminal laws, but the bringing into the world of a child who might become a burden upon the parish in which it was born was an offense. In other words, having a child without being married was not legally wrong but the producing of a child who might add to the sum of public expense was against the law. This attitude, not greatly modified by the passage of time, continued until the beginning of the twentieth century. The changes, legal and otherwise, which have come about, have been largely motivated by organizations of women, who have recognized that the older view of this problem was too severe and that it did not serve the best interests of society.

The first move in our own country toward a change in attitude seems to have been the publication in 1920, by the Federal Children's Bureau, of the first of a number of studies on "Illegitimacy as a Child Welfare Problem." These have done a great deal of good in emphasizing the fact that, in cases of illegitimacy, there is always an infant, which is wholly innocent and has rights, legal and moral, to consideration. I would quote in this connection from a publication of The School of Social Service Administration of the University of Chicago, which deals comprehensively with the question of illegitimate births in the State of Illinois during the year 1928. We find in that year, in a state with more than seven million people, there were 129,668 births. Of these, 2,381 were illegitimate, or 18.36 per thousand. This study indicates clearly that the problem of the unmarried mother and her infant is one of youth, 84 per cent of the mothers being under twenty-five years of age. Forty per cent were under eighteen years, and 11.06 per cent were fifteen years of age or less. Only 7.05 per cent were over thirty years of age. From the standpoint of the most rudimentary humanity, it seems obvious that, if, in one state in one year, there are 2,381 births out of wedlock, and if 146 of these mothers are girls of fifteen years or less, and 787 more of them are from sixteen to eighteen years of age, we have before us a situation which merits the most careful consideration, not only of social workers and physicians, but of every intelligent and socially minded citizen.

The mother and the baby must both be cared for. The insistence which has been made by certain social workers that in all cases the mother be made to keep her child, seems in the face of figures such as those just given, to be ridiculous. What can a child under fifteen, or even the large group of mothers between sixteen and eighteen, do for

the support of an infant unless they have families which are financially able and willing to take the child into their family? This is often not the case.

There seems to have been a definite trend toward a gentler and more merciful attitude on the part of the law toward both the unfortunate unmarried mother and her child. In a decision rendered in one of the courts of the State of Illinois, the following expression seems significant: "The harsh doctrines of the common law which gave an unmarried mother and her illegitimate child little standing or protection, have been modified by the legislature and court decisions of this state."

The very sane conclusion of the excellent study from which I have quoted is that "the child born out of wedlock should be considered first as a child, and accorded at least an approximation of the rights accorded other children." During a service of two years on a committee of the Chicago Council of Social Agencies, which tried to draw up an improved adoption law for the State of Illinois, I was struck with the fact that the infant is not yet adequately protected. As most adoptions are of illegitimately born children, this primarily concerns this group of children. In adoptions, the interests of the child demand that a home be found which is suitable for the child rather than to find babies for homes which are childless. In some cases the latter motive seems to be the ruling one. Adequate protection of the child to be adopted should be provided in all states.

The question which particularly interests physicians is the medical care which this group should receive. Hans Zinsser of Harvard, in his recent book, speaks of the doctor as being so conditioned, by his training, that he is indifferent to social status, morality, or even criminality in those who come under his hand as patients. The unwed expectant mother, to him, is a pregnant woman who presents exactly the same obstetric problem which her more fortunate married sister does. The care of both the mother and the infant afterward may be, and in many cases is, a social problem, to be dealt with by those who are competent in the field of social service. There is a clear-cut need for both efficient medical care and competent help in making such social adjustments as may be needed.

Many illegitimate births have been cared for in "maternity homes," the efficiency of which varies greatly. Some of these are, or have been, poorly run, providing medical care of a mediocre sort. From the point of view of the physician, nothing seems adequate, or just, but proper obstetric care of the sort which may be had in a well-staffed hospital. It should be said that most hospitals have been willing to undertake their fair share of this task. Some facts are quoted in the University of Chicago Report to which I have already referred. The great majority of the hospitals which answered a questionnaire as to their attitude toward the unmarried mother responded that they cared for them. During the year 1928, 877 illegitimate babies, out of 1,346 labors, were born in hospitals in Chicago, while, in the rest of the state, only 283 labors out of 1,035 were cared for in hospitals. In the city of Chicago a few institutions did the bulk of the work, seven hospitals having cared for 655 cases.

While insisting that the obstetric care extended to the unmarried mother and her infant be adequate in quality, neither physicians, who have had experience with these cases, nor social workers, are disposed to insist that all unmarried mothers are wholly worthy women. There are among them some who are irresponsible, lacking in morals and often in intelligence. It is often difficult to make anything more of them than they appear to be at first. Obstetric care and subsequent social help must, however, be given. The social worker, in such cases, has the more difficult task.

Our present economic situation probably is responsible for at least some of the illegitimate pregnancies which occur among girls of a much higher social group. The impossibility of supporting a wife and family upon the income of many young men interferes with marriage and the establishment of a home at an age at which it is physiologically desirable. This, unless young people are entirely separated, and hormonal stimuli being what they are, inevitably leads to an occasional pregnancy. These young mothers may be girls of education, breeding, refinement, in every way capable of fulfilling the responsibilities of wife and mother. Indeed, their potential worth to society may be greater than that of some of those who condemn them most severely. I, and no doubt many of the readers of this JOURNAL, have seen young women pass through an experience of this sort and later occupy useful and respected positions in their respective communities as wives and mothers. The girl should be persuaded not to have an abortion done. It is dangerous and it evades the situation too easily. The man may be more than willing to adopt a course which will immediately free him from embarrassment and all of the danger of which is borne by the girl. She is partly responsible for the existence of the unborn human being, and she should give it a fair deal and not take its life. Abortion is merely adding to the wrong already committed another of greater degree. The difficulty may be solved sometimes by sending the expectant mother to some other place, where the infant may be born, and, if necessary, adopted. The mother may then return without harm to her reputation. This device is somewhat more likely to be useful in the case of the unemployed girl whose parents have some means and who may make it possible for her to live away from home for the necessary time.

The two things which must be accomplished in any illegitimate pregnancy are the safeguarding of the health of the young woman and the preservation of her self-respect. She should be brought back to normal life in good physical condition and with her morale intact if possible. And she should not return, particularly if she is to work, until her strength is entirely restored.

In the case of the very young child, it is difficult to condemn her severely. The blame rather rests upon faulty care and supervision for which the parents are to blame. To assume that she is irreclaimable is an evidence of prejudice rather than justice, especially as young male offenders are labored with in the hope of making useful citizens of them. From the viewpoint of the obstetrician, it is difficult to imagine a group of patients who are more completely in need of proper

obstetric care, and an efficient attempt to restore the child to psychie normality, than these young girls who have been so unfortunate as to find themselves among the unwed expectant mothers.

The leaders in obstetrics in this country believe that the expectant mother and her infant should have the care which is due them. They do not condone immorality, and they regret that any woman, and particularly a young girl, should be in such a predicament. The broadening of human knowledge has brought with it great changes in the manner of dealing with the problems of society. The inadequate and sometimes brutal treatment accorded to the insane in previous centuries has given way, with the development of the science of psychiatry, to a finer, more humane and much more efficient mode of treating those afflicted with diseases of the mind. The increase in the understanding of criminology has changed very greatly the mode of dealing with those who have fallen afoul of the law. The older, more severe, and often ineffective punishments have given way to a more constructive policy in which the desire for rehabilitation finds expression. Those who have fallen victims to alcohol and drugs are helped to regain control of themselves. The effort is sometimes successful and sometimes not, but the desire to help these unfortunates back to normal life is better than a universal condemnation. And success has sometimes paid excellent dividends. The change in the attitude toward the unwed mother and her child, and the presence of the latter must never be forgotten, is another evidence of the wiser, more tolerant, and more constructive attitude of mind which has come with the passing years. The doctor with entire sympathy looks upon the unmarried mother and her child as a problem, both medical and social. Social adjustments can best be made if the mother and her child are in good physical condition. This is most likely to be if obstetric care has been adequate. All of these women cannot be made into valuable members of society. All of the members of the other groups mentioned earlier in this paper may not be fully restored to usefulness. But many can and any physician who has had large experience knows that, in spite of prejudiced statements to the contrary, some may be made into useful women. The fact that so many of them are very young makes it even more important that they should be given a fair chance. May we hope that increasing improvement in social and economic conditions may cause the number to be less in the future.

## VULVAL AND VAGINAL MYCOSIS AND TRICHOMONIASIS

H. CLOSE HESSELTINE, M.D., CHICAGO, ILL.

WHEN the first issue of the *American Journal of Obstetrics and Gynecology* appeared in October, 1920, the clinical entities of vulval and vaginal mycosis and trichomoniasis were unrecognized except by a very few. Within two decades nearly every member of the medical profession of the United States has learned more about these conditions than was known by the earlier best informed specialist. Formerly the belief was current among women that vaginal discharge was associated with marriage and childbearing. Relief, but usually not cures, came from self-prescribed daily douches. This no longer holds largely as the result of scientific study. The major contributions have been made by researchers in the United States. The limited space afforded here necessitates the selection of representative works.

### TRICHOMONIASIS

Vaginal trichomoniasis is an infection (until recently called infestation) caused by protozoa, or bacteria in association with the flagellate. Because Donné identified the vaginal tetratrichomonad in 1837, his name is often associated with it. Controversies over the exact etiologic agent have waxed and waned. Musgrave<sup>1</sup> in 1922 commented that "the part played by the flagella in its (cystitis) production has not been sufficiently studied."

Stein and Cope<sup>2, 3</sup> presented evidence supporting the contention that the trichomonads were pathogenic and recorded that no specific or other bacteria were found. Present-day views agree to the extent that the bacterial flora is not normal; that it is Type 2 or 3. Hibbert<sup>4</sup> transferred vaginal discharge containing trichomonads to normal vaginas, and subsequently introduced a streptococcus with a resultant vaginitis. He assumed the streptococci were pathogenic but did not account for the inability of the bacteria with the trichomonas discharge to produce a reaction. Later Hibbert and Falls<sup>4</sup> obtained favorable therapeutic results with bacterial filtrate.

With a culture of trichomonads free from bacteria and viruses, one could make experimental studies which might answer the question of pathogenicity. Generally, protozoologists have inclined to the view that bacteria may be responsible while most clinicians took the opposite stand. It is possible that it is a combination of both protozoa and bacteria (symbiotic relation) or either.

Bland, Goldstein, Wenrich, and Weiner<sup>5</sup> found a variable behavior of different trichomonad strains. Their cultures grew better above pH of six and well on the alkaline side. It is established that the normal vaginal pH ranges from 4.0 to 5.5 and that the acidity is related to the carbohydrate content of the vaginal epithelium (menstrual and lochial

flow and cervical mucous contaminations excepted). Thus, a depletion of glycogen in the vaginal epithelium favors a higher pH and a more suitable nidus for the infection.

The laborious and meticulous methods used by Hesseltine<sup>6</sup> to obtain pure cultures were fruitless. Yet, within the past year Plass and Trussell<sup>7</sup> succeeded in obtaining a bacteria-free trichomonad culture which has been carried through numerous transplants. Plass and Trussell,<sup>7</sup> by inoculating human vaginas with these subcultures, produced symptoms similar to and findings comparable to the clinical entity of vaginal trichomoniasis. Hesseltine has examined the Plass-Trussell Cultures 2 and 29 and concurs in the bacterial purity. Fragmentary evidence points to absence of viruses. Using these bacteria-free cultures, Wolters and I<sup>8</sup> produced vaginitis as described by Plass and Trussell but not in as great a frequency. This outstanding feat of obtaining a bacteria-free, readily growing culture may break the "log jam" of controversy and open avenues for improvement in therapy. Even so some points are unanswered, namely: (1) under what conditions will vaginitis occur? and (2) why is there an altered bacterial flora when the condition of vaginal trichomoniasis develops?

DeLee<sup>9</sup> published the first report in the American literature in 1920 on vaginal trichomoniasis in which he cautioned against confusion with gonococcal infection, described the macroscopic appearance, emphasized the need of moist slide examinations for diagnostic confirmation, but he was misled in the ease with which the condition could be cured. He relied upon a single or occasionally two or three vigorous scrubings of the vaginal walls, followed by packing with glycerin and soda. In due time, Mathieu<sup>10</sup> confirmed Greenhill's<sup>11</sup> procedure which deviated only slightly from the one DeLee used. Ultimately this painful and traumatic therapy became less popular and has been practically discarded.

Davis and Colwell,<sup>12</sup> and Davis<sup>14</sup> presented a scientific and noteworthy in vitro study of many agents for trichomonadicidal action and then made clinical applications. Their less irritating and less painful cleansing of the vagina with liniment of soft soap and antiseptic powder, creosol douche, and iethyol glycerin tampons loomed promising. Yet Davis warned that persistent treatment for months may be necessary to effect a cure.

Many methods came before the profession with assuring promises too often based on insufficient numbers and inadequately controlled cases; but as requirements for longer periods became obvious, milder and saner practices arose. Kleegman<sup>15</sup> introduced Lassar's paste. Furniss<sup>16</sup> proposed diluted mercuric chloride douches. Gustafson<sup>17</sup> urged sodium bicarbonate douche and glycerin-soda tamponade. The employment of a dry preparation (kaolin, sodium bicarbonate and stovarsol) appealed to Gellhorn.<sup>18</sup> Perhaps to him should go the credit for fostering the dry principle advocated generally today. Still more materials and vehicles had to pass the test, such as hypertonic saline douche by Rosenthal, Schwartz and Kaldor;<sup>19</sup> silver picrate by Winter;<sup>20</sup> quinine by Pattyson;<sup>21</sup> magnesium and copper sulfate by Ruble;<sup>22</sup> halogenated quinolines by Huffman,<sup>23</sup> Zener,<sup>24</sup> Janeway,<sup>25</sup> and Karnaky;<sup>26</sup> various arsenical preparations and finally common sugars

and especially lactose. The postmenopausal case will respond especially well to estrogenic hormone, so said Davis.<sup>27</sup>

Like his many contemporaries, Karnaky<sup>26</sup> has changed from one to another preparation. In controlled series evaluating lactose (alpha or common), it was found<sup>28</sup> that it gave just as favorable responses as the proprietary products. The addition of citric acid was without value and hence is no longer advised. Roblee<sup>29</sup> found beta lactose equally as good. Glassman<sup>30</sup> stated that "the multiplicity of treatment indicates that a satisfactory method is not available." Surely he meant that a simple, rapid, and invariably dependable method was not at hand, for by thorough and complete treatment with one of many preparations most patients are benefited ultimately.

Cures appear to result:

1. From desiccation of vaginal mucosa with powders or tablets.
2. By protection of the deeper or basal epithelium by escharotic action of the surface epithelium.
3. From stimulating the epithelium after the menopause with estrogenic agents to build up into a healthy state.
4. By enhancing a normal epithelium and bacterial flora and replacement of a carbohydrate.
5. By a combination of actions.

All useful therapies by one or another means favor the restoration of a normal vagina, histologically, chemically, and bacteriologically.

Active therapy consists of office and home procedures. The details of the various routines are available in the current literature. Supplementary therapy is the eradication of extrinsic and intrinsic focal sites such as vaginal submucosal lesions, cervicitis, urethritis, cystitis, gastrointestinal or buccal infections, and infections in the sexual partners.

Histologic observations by Adair and myself<sup>31</sup> revealed inflammatory sites and suppuration areas under the vaginal mucosa. Only bacteria were observed, but these multiple lesions might prevent physiologic recovery if therapy was prematurely withdrawn. The ordinary cervical erosions and chronic nonspecific cervicitis respond to desiccation and cauterization by chemical and electrical means, provided it is done under proper indications and with sufficient caution and judgment. Even though several workers believe that the vaginal trichomonads are not found in the rectum, anal hygiene should be prescribed as a precaution. More convincing evidence is needed to establish this point. Sexual abstinence is urgent, because in infrequent instances patients may be reinfected by their partner, according to Cornell and Riba,<sup>32</sup> Drummond,<sup>33</sup> Karnaky,<sup>26</sup> and Adair and myself.<sup>31</sup> If reinfection follows coitus, the male should be studied.

Because many patients with early and mild vaginal trichomoniasis are cured rather readily, extensive studies for focal sites are ordinarily unnecessary, but in instances of persistent or recurring infections, one should make a thorough search. Acidification of the urine and forced fluids may correct a lower urinary tract infection, thus excluding the need for cystoscopy. Allen and colleagues<sup>34</sup> and others called attention to this nidus.

Most of the commonly accepted and employed preparations contain some carbohydrate or glycerin and gelatin for the vehicle or carrying agent and vaginal bacilli thrive in the presence of these, bringing about an increased acidity which is associated with an unfavorable environment for the protozoa and the abnormal bacterial flora. Hence, a direct relationship exists with the vaginal bacilli, glycogen-like content of the vaginal epithelium, increased vaginal acidity and health of the vagina. Moreover, vaginal trichomoniasis is not encountered in vaginas with a rich glycogen-like store and a thick epithelium. Since there is no evidence at hand which suggests that a pathologic hyper-acidity ever exists in the vagina, alkalies should be persistently and insistently avoided.

Vaginal trichomoniasis therapy thus falls into two categories, active and supplementary. Active is that which is directed at eradication of the vaginal condition, and supplementary that which serves to prevent reinfection.

#### VULVAR AND VAGINAL MYCOSES

Yeastlike fungi are the only common fungi producing vulvar and vaginal mycoses. Clinicians by common usage call them monilia and cryptococcus, although the term monilia is botanically incorrect. Practically all the other fungi (leptothrix, streptothrix, actinomyces, blastomyces, etc.), irrespective of the higher, lower, or intermediate forms, produce rarely obstetric or gynecologic disease.

Within less than a score of years, the profession has become cognizant of the common vaginal mycoses of pregnancy and the mycotic vulvitis associated with diabetes mellitus. Formerly these were considered rare and of questionable import. Moench,<sup>35</sup> C. H. Davis,<sup>36</sup> Popoff, Ford and Cadman,<sup>37</sup> and Heard<sup>38</sup> contributed to the rediscovery of this entity. Plass and co-workers<sup>39</sup> characterized the clinical entity by an invariably and constantly present symptom, pruritus, and the common finding of caseous-like material or thrushlike spots in the vagina. Even though the vulva may show considerable reaction, the vagina is the focal site and usually more definitely involved. Other symptoms and findings varied considerably. The pruritus varied from a mild to a most demanding and unrelenting itch, even to the extent of severe sleep disturbances. The acme of the itch coincided with the retiring period and early hours of sleep. It was felt<sup>40</sup> that the pruritus resulted from some by-product of metabolism, such as acetaldehyde or pyruvic acid. Histopathologic<sup>31</sup> study revealed only a superficial involvement of the vaginal epithelium.

Because many women may harbor these fungi without symptoms or clinical evidence of infection, evidence is at hand for the recognition of carriers. To advance proof of pathogenicity Plass and co-workers inoculated pure cultures of this fungi into (1) normal fungus-free vaginas with a resultant mycosis and (2) normal oral cavities of newborn infants with subsequent typical thrush states and fulfilled Kieh's postulates throughout. Later Bland, Rakoff and Pineus<sup>41</sup> amply confirmed these responses to inoculation.

Plass and co-workers<sup>39</sup> pointed out, also, the fallacy of the term, diabetic vulvitis, and offered convincing proof that it is actually a mycosis. Studies later by Hesseltine and Campbell<sup>42</sup> terminated in emphatic confirmation of this stand. The severity of the vulval mycoses in diabetes is related usually to the degree of glycosuria. Furthermore, the vulva has a hyperemic and "scalded" appearance and lacks the caseous material or thrush patches characteristic of vaginal mycosis. The vaginal mycosis of pregnancy and vulval mycosis in diabetes thrives, presumably due to the increase carbohydrate availability of the vaginal mucosa and the glucose in the urine adhering to the external genitals.

Woodruff and I<sup>43</sup> found that the incidence of vaginal fungi (both pathogenic and carrier states) in unselected pregnant patients varied from 14 per cent in better class white to 33 per cent poor class white and to 41 per cent colored groups.

Benham and Hopkins<sup>44</sup> made the surprising discovery that 18 per cent of healthy women harbored these monilia in the gastrointestinal or genital tract. The incidence is lower in men. Dissemination by coitus is unlikely but occurs occasionally.

Fermentation and morphologic studies are a reliable means of identification in most instances if the detailed plan of Hopkins and myself<sup>45</sup> is carried out. Stovall and colleagues,<sup>46</sup> Shaw,<sup>47</sup> Jones and Martin,<sup>48</sup> Weidman<sup>49</sup> and many others have offered their views in this controversial field of identification and are recognized authorities.

Untreated vaginal mycosis of pregnancy practically always runs a self-limited course, terminating at or after delivery, presumably due to an insufficient carbohydrate content after parturition, a behavior noted by Davis and Pearl.<sup>50</sup>

Because mycotic vulvitis occurs so commonly in diabetics, diabetes must be suspected until completely excluded by adequate tests, whenever vulvar mycosis is encountered.

Treatment of mycotic vulvitis consists of diabetic management and local fungicidal therapy. Topical application of 1 per cent aqueous gentian-violet solution daily will usually give complete relief. Applications of diluted Lugol's solution every day or so in increasing strength will likewise cure.

Vaginal mycoses respond to daily applications of 1 per cent aqueous gentian-violet solution if precautions are employed to prevent reinfection, especially from the bowel. The work of Noonan and Hesseltine<sup>51</sup> and Hopkins and Hesseltine<sup>52</sup> pointed out that acids and alkalies are therapeutically not feasible and that element iodine possessed the greatest potency in the presence of serum and cellular elements.

With this information a study was begun<sup>53</sup> and is still in progress in which potassium iodide (0.213 Gm.) and potassium iodate (0.035 Gm.) each are dispensed now in separate (0.5 to 1.0 Gm.) tablets (vehicle of neutralized Kaolin) for vaginal insertion. Vaginal acids react with these two materials to liberate element iodine thus reducing the number of office visits. Gelatin capsules provide a substitute for tablet forms, but sugar and starch vehicles must be avoided. An occasional patient complains of irritation and an infrequent one will have slight vaginal burns from the iodine. Burns and I<sup>54</sup> have

found that single prophylactic applications immediately after birth of 1 per cent aqueous gentian violet to the oral cavity of the newborn whose mothers have vaginal mycoses will reduce remarkably the sporadic cases of oral thrush.

#### SUMMARY

Twenty years ago gross ignorance prevailed on vaginal trichomoniasis and vulvar and vaginal mycoses. Today these conditions are usually recognized and adequately treated although improvement in therapy should and will likely take place. To the physicians of the United States goes priority for most of the important contributions in the understanding of these entities and credit for resourcefulness in the development and improvement of therapies.

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## APNEA NEONATORUM

NICHOLSON J. EASTMAN, M.D., BALTIMORE, Md.

### TERMINOLOGY

ALTHOUGH questions of nomenclature are usually of academic interest only, occasionally a term is encountered which is so inept that it leads to incorrect thinking and an erroneous concept of the condition designated. Deeply entrenched as "asphyxia neonatorum" is in obstetric terminology, there is reason to believe that it belongs in this unhappy category.

Few words have undergone such radical changes in meaning as *asphyxia*. The term comes from the Greek *ἀσφυξία* (*ἀ*, not + *σφύξειν*, to throb) and means literally absence of pulsation. It was used in this sense by Galen to describe the state of an artery distal to a tourniquet and, as late as the eighteenth century, seems to have carried no other meaning. Thus, in 1706 Phillips described asphyxia as "a cessation of the pulse throughout the whole body; which is the highest degree of swooning and next to death"; while Quiney in his *New Medical Dictionary*, published in 1730, defined the term as a "deficiency or privation of the pulse in some cases where it stops for a time." By 1778 the word was being used in a broader sense to convey the idea of apparent death, as from drowning, and in that year an essay by T. Brandt carried the title, "The Cure of Asphyxia, or Apparent Death by Drowning." In a later edition of Quiney's dictionary published in 1794, the earlier definition is entirely deleted and in its place we read that asphyxia "happens from a long failure of vital and animal power, as from drowning." With the beginning of the nineteenth century the import of the word centered more and more on the suffocation which results from drowning, and at the same time its connotation became extended to include suffocation from other causes, such as strangulation and noxious gases. This meaning, of course, has persisted to the present; but when it is recalled that the pulse in asphyxiated animals continues to beat long after all signs of respiratory action have ceased, it becomes apparent that our word *asphyxia* represents a most curious infelicity of etymology.

From a practical viewpoint a much more important objection to the term is the fact that obstetricians have taken further liberties with it and customarily refer to any baby who does not breathe at birth as "asphyxiated," whether the cause be lack of oxygen, cerebral hemorrhage, congenital defect or whatnot. This use of one etiologic condition to denote the whole syndrome of apnea at birth, from whatever cause, is not only illogical but slighted some of the most important etiologic factors. It ignores entirely the gravest cause of apnea, birth trauma, as well as the commonest cause of *temporary* apnea in modern practice, namely, narcosis. Moreover, by focusing attention solely on

the acute anoxic episode at birth, it tends to circumscrive unduly the scope of the problem; in this connection it should be remembered that careful prenatal care and judicious conduct of labor will do more to save babies from apnea at birth than all the resuscitating measures in the world.

In view of these facts, the simple term *apnea neonatorum*, which is merely descriptive and carries no implication in regard to etiology, seems preferable to the older designation. The use of the word *asphyxia* could then be restricted to those cases in which apnea was actually due to lack of oxygen as in, for instance, prolapse of the umbilical cord and premature separation of the placenta.

#### ETIOLOGY AND PREVENTION

*Cerebral Hemorrhage.*—There is general agreement that the most common cause of fatal apnea at birth is cerebral hemorrhage. Statistics also concur in showing that such hemorrhage is most often consequent upon traumatic operative delivery. The procedures which are most likely to produce it are, in order, version and extraction, midforceps delivery and breech extraction (it being assumed that high forceps, which would otherwise head the list, is an abandoned operation). The prevention of grave *apnea neonatorum*, accordingly, consists very largely in the avoidance, when possible, of these operations.

Although clinical and necropsy evidence shows that trauma is the deciding factor in most of these hemorrhages, it is well known that all newborn infants show an especial tendency to bleed and it seems probable that this diathesis plays an auxiliary role, at least, in some of these cases. A rational explanation for this hemorrhagic tendency was advanced in 1917 by Brinkhous, Smith and Warner who showed that the plasma prothrombin level of babies at birth is exceedingly low, ranging from 14 to 39 per cent of the usual adult value. During the past two years Hellman and Shettles, of the Johns Hopkins Hospital, have been exploring the possibility of raising the low plasma prothrombin of the newborn infant by administering vitamin K antenatally to the mothers. They have shown, beyond peradventure, that the plasma prothrombin level of the baby can be raised severalfold in this way, even when the vitamin is given as late as four hours before delivery. The question at once arises, of course, as to the practical value of such a procedure. Will it diminish stillbirth and neonatal mortality by preventing a certain number of deaths from cerebral bleeding? It is realized, of course, that massive cerebral hemorrhage, resulting from severe birth trauma, cannot be prevented by this measure; but it must be remembered that the most common site of cerebral hemorrhage in the newborn is subtentorial, that is, within a small, confined space near the vital centers where a minute hemorrhage may be fatal. To date, Hellman and Shettles have administered vitamin K to more than 500 expectant mothers and are finding that this prophylactic procedure definitely reduces the incidence of all types of hemorrhage in the newborn. Details of the study will appear in an early issue of this JOURNAL.

*Narcosis.*—As we have indicated, the commonest cause of *temporary* apnea neonatorum is anesthesia and analgesia. In my experience, nitrous oxide oxygen pushed (without ether) to the point of surgical anesthesia is a more frequent offender than realized, because of the resultant fetal anoxia. The time element here is most important, and pure nitrous oxide, administered for four to five breaths to produce analgesia, probably causes less anoxia than a mixture of 85:15 continued for five minutes. So far as operative obstetrics is concerned, it seems plain that when nitrous oxide oxygen is given in concentrations of 90:10 or stronger over periods which exceed five minutes, marked degrees of anoxia are produced in about one baby out of every three. The anoxia may not prove harmful, it is true, but in an occasional case it may be associated with profound and even fatal apnea. An adequate saturation of the fetal blood with oxygen can be guaranteed only if the mother receives fifteen parts of oxygen to every 100 parts of the gas mixture, and to satisfy this end, ether should be added to the gas mixture if the latter, in proportions of 85:15, does not suffice. After prolonged labors, in particular, babies seem to withstand anoxemia poorly, and if an operation is necessary in such cases, we prefer ether on an open mask to insure liberal oxygenation of the child's blood. The same is true of breech extractions in which there is an inherent tendency to fetal anoxia due to the impingement of the child's shoulders and head on the umbilical cord.

Since ether passes readily through the placenta, it naturally exerts an anesthetic effect upon the child, and it is this influence apparently, and not anoxia, which causes the occasional "etherized" baby to be slow in breathing. Provided there is no cerebral injury, however, we find that these babies react well to time and gentle stimulation. Certainly, in our opinion, their prognosis is immeasurably better than those in which the apnea is the result of profound anoxia.

We now come to one of the most controversial questions in modern obstetrics, namely: Does the apnea of the newborn which commonly follows the use of modern analgesic programs (barbiturates, paraldehyde, scopolamine, etc.) so jeopardize the baby as to condemn the employment of these drugs? Beyond question, these sedatives, given in amnesic doses, do inhibit the onset of respiration in 40 to 60 per cent of cases, the duration of the apnea varying from a few seconds to half a minute, as a rule. Expediency, moreover, very often dictates the use of outlet forceps in these cases, so that inhalation anesthesia to the surgical degree is superimposed on the drug action, with well-known synergistic effects. If modern analgesia is to be evaluated on the basis of sound obstetrics (dismissing for the time being humanitarian considerations), the following two questions must be answered: Are the babies *permanently* harmed by the temporary apnea? Do any advantages accrue to the baby as the result of such analgesia? Obviously, the first question can best be answered in terms of actual results, that is, by statistics. It is my impression, based on available reports as well as on my own material, that the ultimate outcome for the baby born under analgesia, intelligently administered, is just as good as for one born under no analgesia, provided the infant is mature. Space does

not permit marshaling the huge mass of factual data bearing on this question, but anyone familiar with recent statistical studies of the problem will find this conclusion inescapable. Respiration in the premature baby is at best a precarious business and should not be hampered, in our opinion, by depressant drugs. Turning now to possible beneficial effects conferred on the infant by analgesies, there is a growing conviction on the part of experienced observers that the necessity for difficult midforceps operations arises less frequently in patients who have been given sedation. This is ascribed to the fact that such women enjoy more rest throughout labor and are sometimes better able to rotate the head and bring it to the perineum than a patient exhausted by pain and loss of sleep; such women, moreover, are less likely to suffer from premature operative interference since they are not crying constantly with pain; in other words, the obstetrician is more disposed to give the patient additional time. Whatever the explanation may be, several clinics, including our own, report a diminished incidence of midforceps in this group.

*Anoxia.*—If oxygen determinations are done on the umbilical vein blood at birth, it will be found that most apneic babies (narcosis cases excluded) show very low oxygen levels. This anoxia may be the primary and determining cause of the apnea, as in prolapse of the umbilical cord, for instance; or it may be secondary to cerebral hemorrhage and a number of other conditions which interfere with the fetal circulation and thus prevent proper oxygenation of the blood in the placenta. Since, conversely, anoxia is a common cause of small cerebral hemorrhage, the situation is avowedly a complicated one and it is often difficult to determine positively the primary cause of the apnea in a given case. However this may be, from a practical viewpoint, the most important thing to bear in mind is that most apneic babies *are anoxic*; as we shall see presently, this is the dominant consideration in the treatment of the condition.

*Prematurity and Congenital Malformations.*—Although prematurity is the most common cause of neonatal death, it is seldom responsible for actual apnea at birth unless narcosis or cerebral hemorrhage is superimposed. Similarly, congenital malformations are a more common cause of early neonatal death than of apnea neonatorum.

#### TREATMENT

In the presence of anoxia, apnea is resistant to all types of treatment other than correction of the anoxia itself. In a recent study of experimental anoxia by Kreiselman and myself, even convulsive doses of alpha-lobeline, metrazol and coramine, whether injected intravenously or directly into the carotid artery, were found to have no effect whatsoever on anoxic apnea; on the other hand, a few insufflations with oxygen produced immediate breathing. In other words, there is only one way in which respiration can be initiated when suppressed by anoxia and that is by the administration of oxygen. It is our opinion, therefore, that insufflation with 100 per cent oxygen transcends all else in the treatment of apnea at birth. Attempts to stimulate respira-

tion by adding carbon dioxide to the oxygen are not only futile (since all forms of stimulation are futile in the presence of anoxia), but may even be dangerous; the same applies to the drugs mentioned above.

The main desiderata in the treatment of apnea at birth would seem to be four in number: (1) *Warmth*. These babies are in a state of vascular collapse and should be treated as is any patient in shock. (2) *Posture*. The head should be declined about 30 degrees to favor gravity drainage of fluids in the trachea, but should not be placed so directly downward as to augment a pre-existing cerebral hemorrhage. (3) *Aspiration of mucus*. Clear air passages are essential, and mucus must be removed by means of a catheter, employing either mouth suction or an electric aspirator. (4) *Delivery of 100 per cent oxygen to the pulmonary alveoli*, by adequate apparatus such as the Kreiselman resuscitator. Mouth-to-mouth insufflation, provided it is done gently (never over 20 cm. of water pressure), is usually a satisfactory substitute.

## CONTRACEPTIVE PRACTICES

GEORGE W. KOSMAK, M.D., NEW YORK, N. Y.

ALTHOUGH acknowledged for centuries, the practice of contraception has assumed a different aspect during the past quarter of a century. One of the most signal changes is the acknowledgment of the responsibility of the medical profession in the application of proper and adequate contraceptive measures and their indications. A review of progress, if we may so designate the changes in ideas and technique, is beyond the intentions of this brief article, but attention may be called to the appreciation which has developed in more recent years for the need of controlling and perhaps limiting human fertility under certain definite indications. The indiscriminate, unrestrained, and often unreasoned propaganda of an earlier period no longer prevails. The indications, both medical and social, using the latter term in its wider implications, have been established in a more satisfactory manner, adequate scientific research of means and methods has served to demonstrate the ineffectiveness of earlier procedures, and the thought has gained ground that the physician should exercise his prerogatives in employing contraceptive methods as a part of his legitimate practice. In this connection it has come to be realized that proper concepts depend upon proper teaching and that the medical school curriculum may need to be expanded to include such instruction. However, the fact must also be stressed that control of fertility is no more important than the problem of infertility, for the natural diminution of the birth rate in the higher civilized groups has brought about a fear of depopulation with its evident consequences.

Perhaps this is no place for preaching, but one cannot escape the thought that unless this movement for the artificial control of conception is carefully guarded and regulated, it may in time manifest not only a directly harmful effect on natural population growth but tend toward a resolution by men and women not to accept their responsibilities towards childbearing. It is fortunate that the modern eugenist has come to an appreciation of the import of these questions.

Whether procreation can or should be regulated is a problem in the minds of many people; it is no longer an academic question. There is a firm conviction on the part of the public that childbearing is a matter which they want to decide as individuals. We must differentiate this from the conception by which pregnancy is regarded as merely undesired or inconvenient.

Physicians have not constituted in the past an active or influential force in guiding sane and legitimate contraceptive practice in the proper direction. They have failed to realize the importance of the movement and have done little to overcome the hysteria and exaggeration which have characterized the former agitation for "birth control"—a term

which is an unfortunate misnomer. As regards the excesses in the propaganda for the latter, I would like to repeat here what I have said on other occasions, namely that the wider employment of contraceptive measures has not brought about that unalloyed state of bliss which the earlier enthusiasts and exploiters had promised. The doctor was looked upon by them as an obstructionist when, as a matter of fact, he was merely a doubter. However, that viewpoint is changing. If contraceptive practices are properly employed in a preventive sense, in cases of maternal illness, in over-fertility (especially when associated with definite social implications), and as a possible method for spaced parenthood, then the physician and no one else should be the guiding and directing influence. If he declines to assume this function because of inherent personal objections or religious belief, that is a matter for his own conscience and for this attitude he should not be condemned.

The last twenty years disclose a gradual change in sentiment towards contraception as a legitimate responsibility of medical practice. However, much remains to be done to place it on a more definite, scientific, and social basis, with appropriate research directed to means and methods and the problem of their evaluation.

The efforts, often well meaning, but frequently misguided, which have been employed to distribute contraceptive advice to the public must, in my opinion, be largely revised in order to label them as a medical activity and to free them from the purely propaganda aspects of the movement. The latter has had its bad effects; we need not discuss them further, nor need we dilate upon the subject as it affects the private practitioner and his patients. It is in the so-called "clinics" which are accessible to the general public that reform is necessary. These have multiplied in recent years and are largely "extramural," so far as they have no connection with established hospitals and, because of diversified legislative restrictions, are operating usually without the pale of the law. Unable to secure legal recognition, they are unlicensed and therefore uncontrolled by any supervising authority except the local policeman. If such clinics are needed for the medically indigent, they should be made an essential activity of an established hospital and removed from the domain of a doubtful sentimentality or misguided propaganda.

"Contraception," unfortunately labeled "birth control" is a proper subject for medical thought and discussion, which, however, has prominent social aspects. In the near future we will have to come to practical conclusions as to the manner in which the problem must be solved and the physician must be prepared to assume his responsibilities, he must study it, he must guide it, he must not be a mere obstructionist. Even with the time and thought given to the development of adequate, harmless, and effective methods of contraception, it cannot be claimed that anything like satisfaction has been attained in this field. This may be contrary to the claims of enthusiastic propagandists and manufacturers of appliances, but it is quite true nevertheless. Recognized authorities in the research field have many accomplishments to their credit during the past twenty years and legitimate organizations and institutions have endeavored to develop a sound basis of study

and investigation, but much remains to be done to eliminate the unfortunate and often hysterical aspects which have characterized the movement in the past. "Birth control" in the generally accepted, popular sense, is not a panacea for the evils of this world.

A development of particular interest in recent years is the public health aspect of contraception. Both local and state organizations have given this official recognition, and clinics are supported by public or private funds. "Mothers' Conferences," "Marriage Consultation Centers," and similar euphonious terms are employed to overcome possible prejudices. A recent survey lists, in 1939, a total of 166 clinics in some 20 states, in most of which, it is stated, advice is given on medical grounds only; in others economic and social circumstances suffice.

If public health departments have given careful recognition to the movement as a part of their services, it is difficult to reconcile their activities with established Federal statutes. It would seem that the time has arrived when outworn legal restrictions should be abolished or at least revised in conformity with professional standards and scientific practices.

There is a sane and an insane approach to the problem of contraception—it is to be hoped that within another decade or two, an adequate solution may be reached.

## THE EVALUATION OF HOSPITAL STATISTICS

GEORGE GRAY WARD, M.D., F.A.C.S., F.R.C.O. & G. (HON.),  
NEW YORK, N. Y.

**T**HE first function of a hospital is the care and cure of the patient. Codman's statement that, in the past there has been no attempt to systematically fix the responsibility for the success or failure of each case treated and that in most hospitals no responsible person or department is assigned to investigate the efficiency of treatment, is a truth that makes self-evident the compulsory need of an adequate follow-up system for end result study.

Evaluation of the results of treatment cannot be based on the condition at the discharge from the hospital alone but must be determined at the end of a definite period of observation. This necessitates a properly organized system of follow-up which, since Codman's appeal, is coming more and more into use as an integral function of every Class A hospital in accordance with the requirements of the American College of Surgeons.

Still there is much room for improvement and further development in follow-up statistical study. This applies to obstetric and gynecologic patients as it does to other groups of medical and surgical illnesses. The first essential and underlying requirement in a reliable follow-up system is accurate case histories. All our deductions as to results are of value in direct proportion to the accuracy of the records. Carelessly recorded case histories are far too frequent in many hospitals and every effort should be made to simplify history taking and to secure uniformity. We have endeavored to accomplish this in the Woman's Hospital by having a printed form, which includes all the essential facts required, placed on the margin of the history sheet as a guide for the interns and residents when taking histories. To secure uniformity for comparisons, the Standard Classified Nomenclature of Disease, in use in most American hospitals, is employed.

Dictation of operative procedures made at the time instead of days or weeks later is important to insure accuracy. Surgeons' bedside notes as well as nurses' notes should be part of the record. A summary sheet at the end of the record, containing in brief all the essential facts of the case with the signature of the surgeon in charge approving the history is of great value.

Contact is made with the patient while in the hospital by the Social Service Department, which directs her to report at the follow-up clinic for a definite period of observation.

The follow-up clinic should be compulsory for each surgeon and his assistants. The success of the follow-up depends upon the fact that the surgeon who is in charge of, and who operated upon, the patient will see and examine her.

There should be definite rules for the visits to the follow-up clinic, depending upon the type of case. Simple laparotomies, hysterectomies,

etc., should be under observation for a year, making three or four visits before a final classification as to the result obtained is made. Plastic cases, such as prolapse, may require a more extended observation to determine the final result, while minor cases may be followed for a shorter time. The visits and results are recorded on an end result card which contains a summary of the case.

At the end of the period of observation the cases should be classified as successful, partially successful, or failures, and this should not be based on the anatomic result of the operation or treatment, but upon *whether the patient was cured of the complaints for which she sought relief.*

The obstetric follow-up has a somewhat different problem than the gynecologic. It is not necessary, or practical, to have the postnatal patients return for so long a period, but we can get both the mother and baby to come back for observation at monthly intervals for three months. If there is a postnatal displacement of the uterus, lacerations, or erosions of the cervix, the patient can then be referred to the gynecologic department.

Chartered accountants are universally accepted as essential in checking hospital finances, so professional statisticians are also necessary to evaluate properly not only the general mortality results of hospital care, but to study the mortality and morbidity rates of the personnel of the staff, and of the types of treatment employed in the various diseases and conditions cared for.

As it is an established custom to have a financial audit made, surely where we are dealing with human lives and health we should employ as careful methods as in the case of our dollars. This, however, is rarely done.

For the past twenty years such an accountant's audit has been made each year by professional statisticians for the Woman's Hospital, and a report rendered which is illustrated with colored graphs and the associated figures. To secure an accurate and complete audit, professional statisticians must be employed. Compiling of hospital statistics is usually delegated to a nonmedical clerk, perhaps supervised by one of the medical staff, and is of a quantitative, not a qualitative, character.

At the end of each year the statisticians have placed at their disposal the entire case histories of the discharged patients, which are studied, the facts required tabulated, and the report compiled. In the beginning it was a pioneer work, as we had to feel our way and establish rules for procedure, and make definitions in order to insure an accurate interpretation of the results. From time to time changes in these had to be made.

Some of the basic rules upon which the audit is made are as follows:

The number of cases *discharged* during the year has been made the basis for computing death rates, *not* the number of *admissions*.

Each stay in the hospital is considered as a new case for statistical purposes, on the assumption that each time a new risk is involved for the hospital staff.

An operation is credited to the surgeon performing the operation.

In the event of two surgeons operating, the one who has the responsibility is credited with the operation.

Where a junior surgeon operates against his will at the direction of his senior, the responsibility for the result must rest with the senior provided the junior registers his objection.

Operation by house surgeons are always done under the supervision of an attending surgeon, and therefore are credited to the supervising surgeon.

Classification of surgical risks, as *good, fair, bad*, is taken into consideration in evaluating mortality rates of individual surgeons.

A distinction has been made between operations and operative cases, as some patients have more than one operation during a stay in the hospital.

The ratios that have been derived by measuring postoperative deaths against these two bases have been called, respectively, the "fatality of operations" and the "mortality of operative cases."

The disposition of all surgical cases discharged out of the hospital *without* operation should be accounted for in the hospital report, otherwise a hospital's low mortality rate may be due to a refusal or transfer of poor risks.

The audits submitted annually in the form of graphs and charts depict the trend each year of the cases discharged, the death rates, the total ward and private cases of each member of the Staff and of the courtesy surgeons. These are likewise detailed separately for the gynecologic and obstetric services, with notations of recoveries, morbidities and mortalities, character of wound healing, etc., in the former, and in addition the outcome of pregnancies, types of operative deliveries, complications of labor, and fetal results in the latter.

A continuing oversight and study is thus provided by which the work of the hospital and the activities of the individual members of the Staff can be evaluated from year to year.

#### COMMENT

The mortality and morbidity results of a hospital staff, and the percentage of successes, partial successes, and failures of certain lines of treatment are of the utmost importance in influencing the trend of our practice and therefore the health of the community. The value of these percentages must be based upon the reliability and completeness of our records.

A successful follow-up clinic depends upon the fact that the surgeon who operated, or was in charge, will examine the patient. If the patient knows that she is going to see "her doctor," she will come back for a check up, but she will not return with the same readiness if an intern or assistant is to pass judgment upon her.

These end result studies of a follow-up clinic are of great value to the patient, to the surgeon, and to the hospital. For the patient, mortality and morbidity are reduced; for the surgeon, his illusions are dispelled; and for the hospital, greater economy.

The economic value of end result study is incontrovertible. The surgeon becomes more proficient and is stimulated to greater efforts and to the correction of faults.

The days saved to the patient and to the hospital by more speedy convalescence, mean money saved to both patient and hospital.

There is the same need for auditing our surgical results as there is need of auditing our finances.

There is a need to establish standards for comparison of results, and this auditing is as necessary for the leaders of the profession as it is for the rank and file.

Our experience with the employment of a professional statistician to audit our results has confirmed most positively our opinion that such a procedure is not only a great advantage in facilitating the compilation of our statistics, but is an essential warranted by the great importance of a serious problem. It has shown us that the usual methods employed by hospitals in compiling their mortality and morbidity statistics, without proper qualifications and definitions, are practically valueless for comparative purposes.

I fear our sense of surgical responsibility too often lies dormant, lulled into a peaceful slumber by the droning of tradition and the warmth of self-satisfaction. The stimulus of light is needed to awaken it, so that the "Golden Rule" may be lived up to. That light can only come from an honest auditing of our results.

I am convinced that a comprehensive accurate surgical audit, made by those who have professional statistical training, will be the means of saving many lives, much suffering, and much money.

## THE INCREASE IN HOSPITAL DELIVERIES

E. D. PLASS, M.D., IOWA CITY, IOWA

DURING the past two decades there has been a marked reaction against the old traditions that babies should be born at home; each year has seen an increasing percentage of hospital confinements. This tendency has been deprecated by many older practitioners who still insist that hospital delivery is not only more expensive but more dangerous, since the patient is subjected to contact with infectious agents and other influences against which she has no effective defense. So far it has been quite impossible to evaluate the claims of the rival groups; the proponents of each concept being quite irrevocably convinced of its virtues. There are, however, certain phases of the problem which may be considered with reasonable objectivity.

There can be little doubt that home delivery, reduced to its bare necessities, is less expensive than hospital confinement, and will therefore continue to be the choice of those for whom economic considerations are paramount. On the other hand, the expense of providing in the home conditions at all comparable to those available in any good hospital weighs the scales in favor of the latter. Nursing care, even by a single trained nurse, additional domestic help, medical supplies, and other incidentals undoubtedly cost more than in the hospital where everything is supplied economically on a mass basis. In the larger cities, another factor, limited and unsuitable small apartments, almost compels institutional care.

It is probably true that uncomplicated deliveries can be conducted safely at home, but when complications arise, the advantages of hospital facilities are undeniable. The major obstetric difficulties, obstructed labor, severe toxemia, hemorrhage, and obscure associated disease can only be handled adequately in a well-equipped hospital where operating equipment, dietary and laboratory facilities, transfusions, and prompt consultation are available. The development of any one of these serious complications constitutes a real argument for hospitalization.

Statements by older physicians that they have delivered three or four thousand women in their homes without a single maternal fatality and with a negligible fetal death rate do not stand close scrutiny. Either their serious cases were transferred to a hospital and the ensuing death charged to the institution, or a nearby practitioner was called in toward the end and each involved physician claims that the other should bear the responsibility. In any event, statistics still show that maternal deaths do occur in the homes and in hospitals among patients who were treated originally at home and admitted to the institution in extremis.

It must be admitted that many busy physicians, and especially the specialists, prefer or demand admission to a hospital for other and more personal reasons. They need spend less time with each patient who is

always under competent supervision by the nursing and resident staff and can attend to other duties during the earlier stages of labor with the assurance that their instructions are being observed and that the patient is not being neglected. They can call for trained assistance and special technical therapeutic agents when the need arises. They can provide excellent anesthesia of any desirable type and can safely give considerable pain relief by the use of analgesic drugs. By and large, hospital delivery is easier on the attendant, who can not only give better care to individual patients but who can give more women the advantage of his skill and experience.

The more serious dangers attached to hospital confinement are those inseparably linked with the availability of the very facilities which make it a life- and health-saving refuge. The operating room and its many instruments may have an irresistible attraction, which is further enhanced by the presence of modern anesthetic agents and trained anesthetists. Operative delivery is easy on the accoucheur, it saves his time, and, moreover, enables him to acquiesce with the family's demand that he "do something," and thus augments his local reputation and expands his ego. His unfortunate results are covered by alibies, the falsity of which are not realized by the relatives, who are told that everything possible was done: the baby who died of intracranial hemorrhage had "congenital heart disease," the child who died from maternal overdrugging with sedatives or oxytocics had the "cord around the neck," the mother who failed to survive had "pneumonia" not puerperal sepsis, "heart disease" not shock.

Within the past few years an intelligent attack upon this problem has been made in many of the larger hospitals through the development of an organized obstetric service. Staff members are chosen from those who have had adequate special training and rules are developed and enforced, seeking to safeguard the patient. Major operative procedures cannot be done without preliminary consultation with a staff member except in grave emergencies, and members of the courtesy staff must submit to supervision of their work by those in the permanent organization. The advantages of such a system are obvious even though it attacks the rugged individualism of the physician, a hold-over from the horse-and-buggy days when the profession had not been integrated and special ability was not so highly developed. It can easily be shown that here as elsewhere in medical practice there are definite advantages in consultative discussion and in therapeutic restriction in the interest of safety.

The past ten years have shown a considerable and encouraging decrease in maternal mortality generally over the country. So many possible etiologic factors enter the picture that their individual evaluation is impossible. Letter and more uniform prenatal care undoubtedly has played a major role even though it is still frequently of a sketchy and inadequate character. The organization of circuit and intramural courses of instruction has created a renewed interest in obstetric problems and has disseminated more widely the recent advances in the care of maternity patients. The improvement and enlargement of facilities

for training obstetric specialists and their certification by the American Board of Obstetrics and Gynecology have made expert attention more widely available. The activities of the Federal Government, through the Children's Bureau, have enabled the States and their subdivisions to provide certain facilities previously denied those in the lower economic groups. The American Committee on Maternal Welfare has worked through its state and county components to raise the character of prenatal supervision and the quality of general maternity care. Clinical and laboratory investigators have thrown new light on obstetric problems and have developed improved methods of treatment which are widely disseminated through the medical press. The public has aroused itself to the deplorable and preventable conditions which formerly prevailed and has demanded that the situation be improved. The younger, child-bearing women of the present tend to ignore the providential character of maternity and to take an intelligent interest in their reproductive careers and to demand more adequate care. Hospitals have become widely available over the nation and are being used increasingly by obstetric patients, as their facilities for adequate care improve under the stimulation of the American Medical Association, the American College of Surgeons, and other interested bodies.

It would be too arbitrary to assign relative values to any of these various factors but undoubtedly equitable to state that they have conjointly been largely responsible for the diminution of obstetric mortality. It also seems quite indisputable that the hospitals have had a considerable role in this encouraging development, depending upon the organization, ability, and conscientiousness of the attending staff. The small, inadequately equipped institution with no staff organization and no specially trained personnel probably offers no real advantages over the home and may even increase the hazard by encouraging radical and ill-advised operative deliveries and other dangerous procedures. On the other hand, the better institutions with their modern facilities, alert and progressive staffs, consultation requirements, trained supervision, and a critical attitude toward their accomplishments constitute an important factor in the provision of complete and adequate maternal care. The expansion of such facilities should further decrease the number of preventable maternal and infant deaths.

In conclusion, it may be offered that the trend toward institutional delivery is sound and its expansion inevitable, provided the hospitals continue to improve their equipment and personnel, and agree to such restrictions on individual initiative as are most conducive to the greatest safety for the mother and her child.

## THE APPLICATION OF SCULPTURE TO PRACTICAL TEACHING IN OBSTETRICS

ROBERT LATOU DICKINSON, M.D., NEW YORK, N. Y.

FOR telling effect and minimal mental effort only three-dimensional instructions can adequately demonstrate certain bodily functions and several structural relations. Chief among these is mechanism of delivery. And herein there is every reason for combining high art of sculpture with scientific research, whether this instruction be for medical college or for popular teaching.

In 1886 I enlisted the aid of the sculptor, J. Massey Rhind, in making my scale models of the pelvis and fetal skull; made teaching models with pessaries;<sup>1</sup> others of the complex relations of the pelvic floor and the related organs;<sup>2</sup> and later used flexible models of perineal lacerations for students to repair.<sup>3, 7</sup> Since last year that distinguished pupil of our great anatomist Huntington, the sculptor who has made so striking a contribution to anthropology for the Hall of Man in the Field Museum, Malvina Hoffman, has been counsellor in this presentation of the stages of labor. She helped secure the services of Abram Belskie, who has been willing to harness his fine talent to the slow pace of extreme exactitude in scale and finished detail in tissue.

The goal in view was a forthright change from the slumped and relaxed state of post-mortem sections heretofore copied for obstetric pictures in textbooks to the *alert upstanding tensions of the living*, as depicted in x-ray films, taken at each stage of active labor. Very special exposures are included for this series, such as those of the *ascent of the external os nearly to the inlet*, while several unpublished studies are incorporated, such as those of the thickness of the uterine wall, the location of the placenta, the projection of the forewaters, the relation of arms and legs. I am deeply in debt to the great collection at Sloane Hospital (4,800 patients); to the Obstetric Departments at Yale and Johns Hopkins; and to the studies at Beth Israel and Harlem Hospitals. Drs. Caldwell, Moloy, Thoms, Dipple, Snow, and Ball have made possible the live look of our sculptures.

For the notable thickness of the pelvic floor shown in Fig. 1, all of the full-term sections of the region, including those of Canton's great unknown Argentine atlas,<sup>4</sup> were traced or drawn to full scale and then superimposed, demonstrating a striking similarity, except for two instances. The extreme thinning of that massive structure seen in Fig. 2 is the result of my study of 1882, wherein I let the advancing head mold the thinnest possible lead sheet between it and the perineum; then against the metal I could insert a puncturing needle to measure the attenuation to 4 or 2 mm.<sup>2,7</sup> The "Birth Prelude" disc on the stages of fetal growth is worked out mainly from Seammons and Calkins,<sup>5</sup> and the embryology under counsel from Streeter.<sup>7, 8</sup>



Fig. 1.—At term. Woman in median section, child in full round. Cast in terra cotta plaster from plasticine original. Thickness of pelvic floor carefully studied.

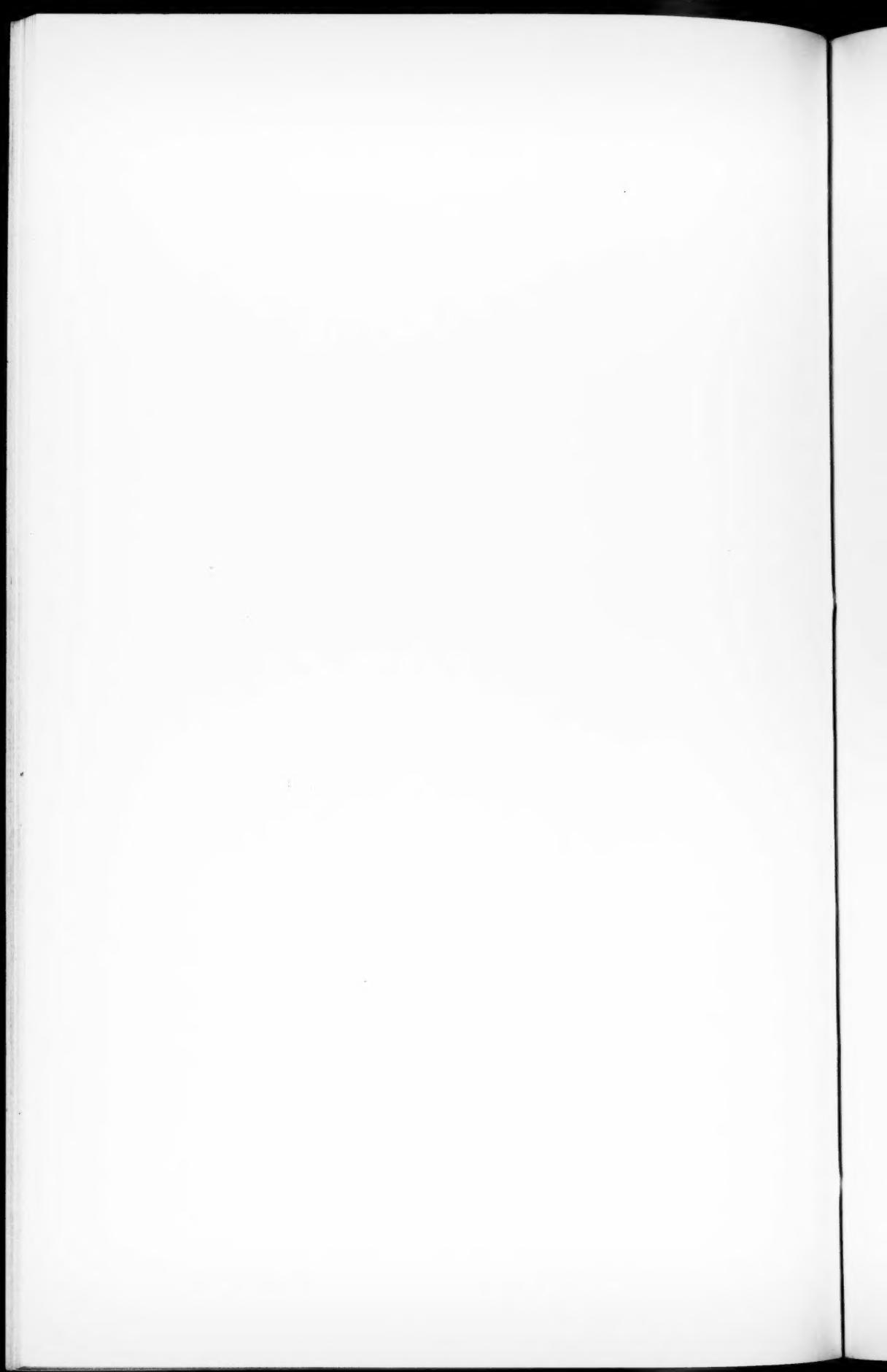




Fig. 2.—Head crowning, abdominal muscles active. Thinning of pelvic floor demonstrated.

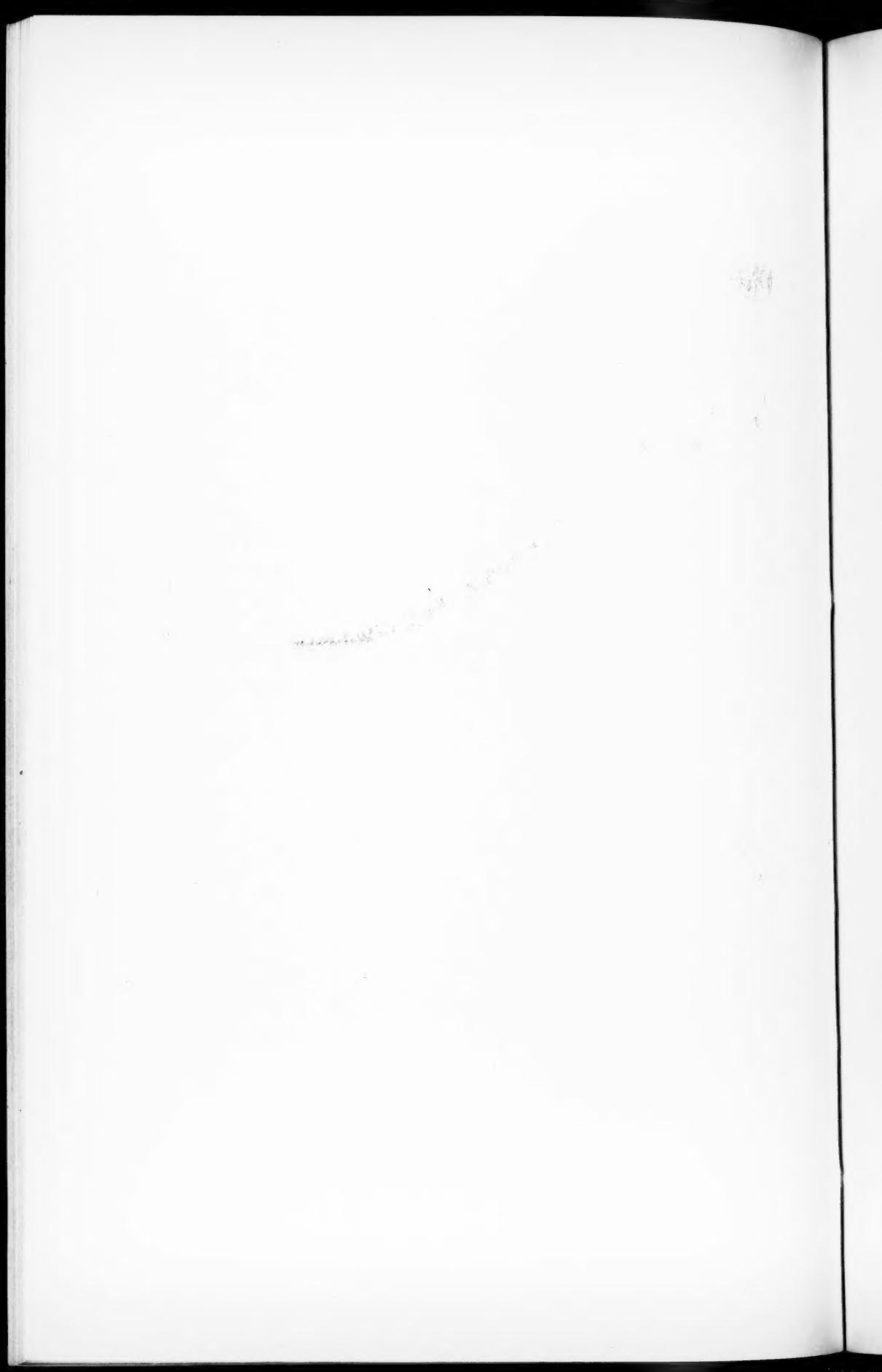
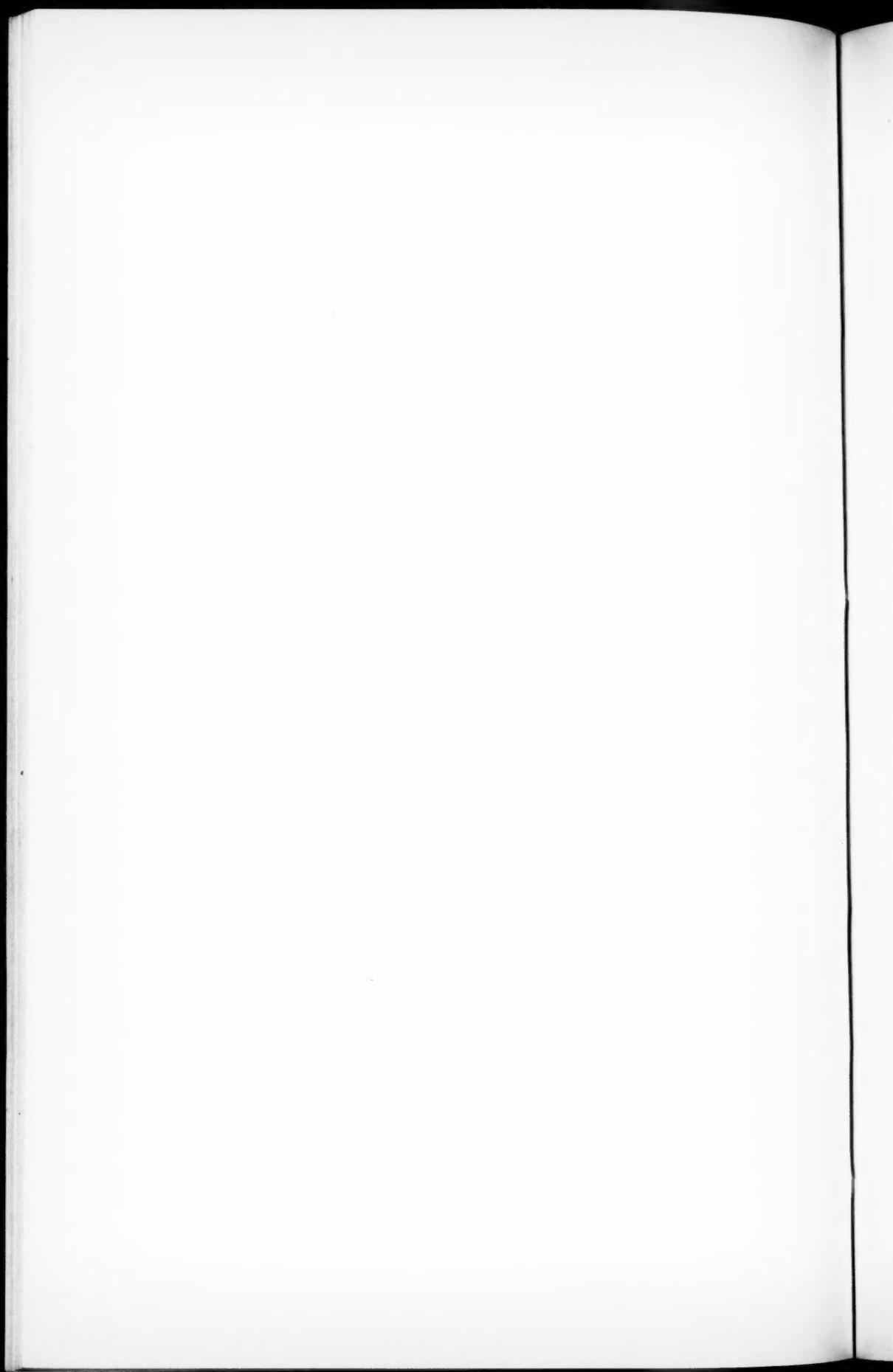




Fig. 3.—Ten-panel model of stages of labor (25 by 39 inches). Provided with box whose doors carry diagrams fully labeled, as a kind of triptych, and called Birth Relief.



Except for the three-foot panel of stages of the ten-day trip down the Fallopian tube and some embryos, the entire presentation is of average dimensions carefully estimated by a special research. One modification, however, is the panel nearly four feet by two (Fig. 3) of 10 sections in full relief, on a scale of halved dimensions. Herein are certain noteworthy contrasts of importance: (a) that between the uterine cavity before labor and the total distended birth canal, because the models of the babies are removable; (b) that between the head imbedded and molded; and particularly (c) that between the full-term flexed fetus and its elongated sausage shape just before its exit.

The frontispiece shows the three-foot disc called "Birth Prelude," with eleven stages of growth, life size, all labeled. The spiral form was chosen for compactness and decorative quality because of the awkwardness of the usual horizontal presentations.

This initial "Birth Series" comprises 18 models in terra cotta plaster. There are 9 stages of growth, 6 steps of labor, including placental expulsion, then the empty uterus, and one stage of involution. There are nonpregnant normals of the pelvic contents in median section, and the same displayed and sectioned transversely. The embryos, *in situ* (and enlarged), take up weeks 4, 6, 7, 10, and 14 (menstrual age) and demonstrate also placental site and circulation.\*

Applicable in principle to these and other models is the very timely plea made by Kosmak concerning the effectiveness inherent in simplicity and directness in medical illustrations. Also his warning against the prevalence of that clouding and overshadowing of essentials by detail that often obliterates the point of the picture, what he calls "landscaping" and "artistic, valueless trimmings," which I call showiness and prettiness.

The principles involved in the problem thus raised might be enumerated as follows: Use of the simplest form capable of conveying the idea. Dependence on outline alone, or diagram, whenever sufficient. Line drawing for zinc cut when rounded surfaces call for shading or tissues demand detail. For certain delicate gradations or polished surfaces, otherwise difficult to depict, drawings by brush, crayon, or stump, for halftone reproduction on coated (glazed) paper at the higher cost both of cuts and book. Where three-dimensional representation can alone adequately teach, use of models, as for steps of operation or stages of labor.

To these other requirements may be added. Thus we emphasize the following: Scale in relation to life to be a primary consideration for every photograph, drawing, or model, with invariable statement of that scale. Each series, or each set of steps, to be shown on the identical scale, and so reproduced. Labels to stand close to, or even on the part, if not defacing, or on lateral margins with connecting line. Diagrams to accompany the illustration if original is less than clear, as in very many x-rays. Also when letters or numbers or lines would

\*An atlas, full size, of the models has been issued by the Maternity Center Association.

obscure or spoil the illustration. Color to be used as often as is essential to understanding or good teaching quality, if cost can be met.

The best results can be gotten with that close co-operation between author and artist that is found, but is oftentimes absent. The author should always assemble all data and abstract them, such as measurements, and hunting out the best previous illustrative material. He should make sketches, even if crude, and space his lay-out. If he can make one original to set the pace, he gets what he wants across to the artist, especially in detail of anatomy, in the instance of these models, in presentation of bone or fat, uterine wall, twist of cord. To the artist he leaves beauty of form of limb and hand and foot, but, with each, provides measurements to the millimeter. The final check on dimensions and finish is the author's and he is fortunate if he can make the ultimate corrections, matching the artist's touch. For repetitious areas, such as bone or muscle, the work can be done with economy by an art student. This making of example and finish, and some full models, has been my part.

Models involve relatively high cost, compared with the best drawings, until the demand for a given series lowers the rate. The museums of natural history give to medical instruction examples of highest effectiveness with maximum attractiveness and appeal, by full-form, full-texture, full-color presentation. It will be noted also that feeling of actuality is conveyed completely only thus in the round, and to such an extent that photographs of models convey this feeling as few drawings succeed in doing.

Aided by funds from Maternity Center Association, Field Museum, National Committee on Maternal Health, and the studio facilities of the New York Academy of Medicine.

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## THE DESIGNATION OF SPECIALISTS BY THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

WALTER T. DANNREUTHER, M.D., NEW YORK, N. Y.

THE progress made in the diagnosis and treatment of various groups of illnesses has gradually impressed upon both the public and the medical profession the desirability for qualifying specialists by some recognized official body. A certificate of specialization based on training and a comprehensive personal examination can be recognized as evidence of adequate qualification, in contradistinction to the self-styled "specialist." This distinction would seem to apply with definite significance in the field to which this JOURNAL is devoted, particularly in obstetrics, in which inexpert interference with the natural progress of normal labor, with its undue increase of operative deliveries, has contributed materially to the high puerperal mortality rate.

The American Board of Obstetrics and Gynecology was conceived in the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in September, 1927, fostered by the American Gynecological Society in 1928 and by the Section of Obstetrics and Gynecology of the American Medical Association in 1929, and incorporated in 1930. The chief objectives of the Board are to elevate the plane of obstetric and gynecologic education, training, and practice, as well as to fix standards for justifiable specialization. The primary purposes were to encourage and induce potential specialists to prepare themselves thoroughly, to persuade medical schools and hospitals to provide adequate facilities for special training, and to put the stamp of approval on qualified specialists. The principal function of the Board is to conduct examinations designed to test the qualifications of voluntary candidates for certification. Whereas in some quarters the Board's motives were originally viewed with suspicion, the quiet efficiency of its operation during the past ten years has dissipated practically all of the previous antagonism. Whatever momentum the activities of the Board have gained has been due largely to its successful accomplishments. The necessity for abbreviation precludes a review of many of the details of the Board's work which would clarify all of the misconceptions which still prevail.

Each of the sponsoring organizations was and still is represented by three elected members, who are also directors and examiners. There have been two changes in personnel during the past three years. Too frequent replacements are undesirable, because previous experience is of inestimable value to an examiner. The Presidency of the Board is of no significance whatever, as the sole reason for selecting officers is for the orderly transaction of business. All nine examiners serve on exactly the same basis, except the Secretary. The scope of his duties is shown by the fact that during the past fiscal year his office handled thirty-two thousand pieces of mail and prepared the first edition of the Di-

reductory of Certified Specialists, in addition to functioning as the focus for all routine matters. No one other than a Board member can fully appreciate the amount of work which devolves on each one throughout the year. All but the President are appointed to various committees: Credentials, Examination, Budget and Finance, and Graduate Training. Each one reads innumerable written examination papers and case records for many months before the oral and practical examinations are held. Although mistakes have been made, the examiners have labored faithfully, unswerved by extraneous influences, favoritism, or prejudice, and regardless of censure or applause.

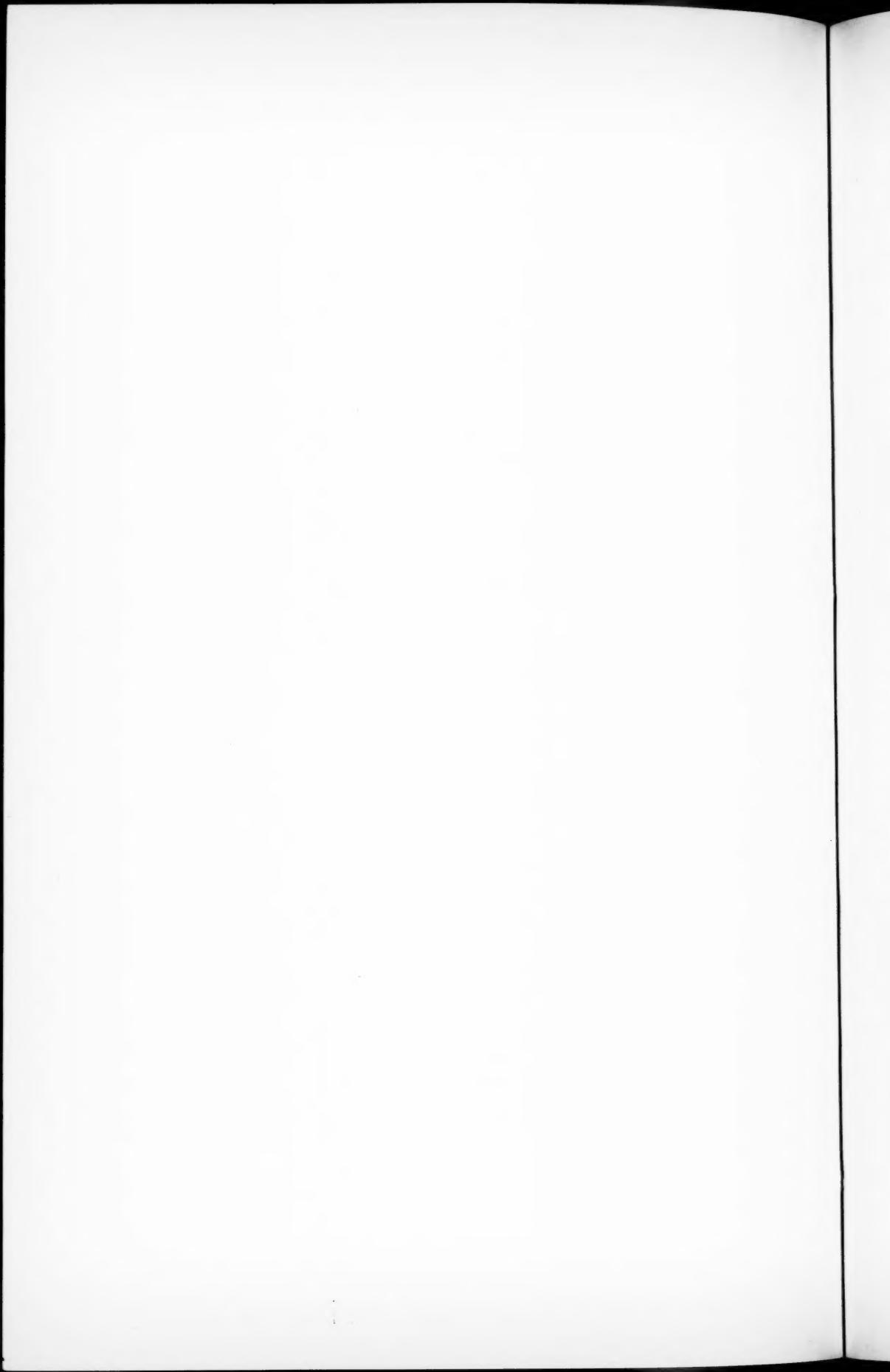
Between September, 1930, and January, 1932, 255 recognized obstetricians and gynecologists were certified on application without examination. Each of these was either a Fellow of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, or the American Gynecological Society, and limited his practice to obstetrics and gynecology, or held a professorial appointment in a Grade A medical school, or was so distinguished clinically that he received the unanimous vote of all nine Board members. The future significance of certification was apparently unanticipated by many others who might have been so certified, but who failed to file an application before the lists were permanently closed.

Since 1930, the Board has examined 1,226 applicants, of whom 992 passed and 234, or 19.1 per cent, were rejected. The total number of diplomates of the Board to date, including the 255 certified without examination and 992 who successfully passed the examinations, is 1,247. The value of every certificate issued depends not only on the maintenance of high standards by the Board, but also on the character of the practice of each diplomate. The license to practice medicine indicates that its holder is competent to assume any professional responsibility which he chooses. A certificate of competency only would be a trespass on the prerogatives of the State. The Board recognizes that many general surgeons do excellent pelvic surgery, and that many practitioners are well qualified to carry on a large obstetric practice, but these men do not claim to be specialists and require nothing more than a license from the State. On the other hand, if an obstetrician or gynecologist announces himself as a specialist, his pronouncement should assure superior training, extraordinary skill, and a background of extensive clinical experience. One hundred and two formal applications for examination have thus far been rejected by the Committee on Credentials. Certification carries with it the implication of absolute specialization, and the Board has a right to expect that its diplomates will restrict their work to obstetrics and gynecology. Each can help to preserve the prestige of his certificate by forwarding to the Secretary's office specific information regarding those who fail to limit their activities. The Board is prepared at all times to revoke the certificates of those who are found to be making excursions into other fields of medicine, and has already dropped the names of six such offenders.

With the passing of time, and as the Board gained experience, the necessity for changes in procedure became obvious. First, an adequate examination fee is essential for the conduct of the organization. Whereas the fee was originally fixed at fifty dollars, after ten years of operation it became necessary in 1939 to increase this to one hundred dollars. Second, when the yearly number of applicants exceeded two hundred, as it did in 1938, the custom of holding a written examination twice yearly was found to be too cumbersome, and was discontinued. Third, the large number of candidates in the past four years has made it necessary for the Board to utilize the services of nine assistant examiners during the four days of the oral and practical examinations. These were wisely provided for in the Articles of Incorporation, and care has been exercised to invite only those who hold professorial positions in Grade A medical schools.

Two radical changes will become effective on January 1, 1941, after which three years of special training in seven, instead of five years of practice, will be required before an applicant is eligible for examination, and all applicants without exception will have to file case records and take a preliminary written examination before appearing for the oral examination. As a result of the present trend toward prolonged institutional training, the Board has recently encountered several candidates who could fulfill the existing requirements for eligibility, but who had not as yet carried the responsibility for personal private patients. On the other hand, the Board feels that within the ten years of its operation, all senior and experienced obstetricians and gynecologists have had ample opportunity to apply for certification, and there is no longer any reason to make a distinction between candidates.

The achievements and progress of the Board since its creation have been such as to make its influence felt throughout the country. Prospective applicants for certification are preparing themselves more thoroughly for the practice of obstetrics and gynecology, hospitals are demanding certification for appointment to responsible staff positions, certain medical societies are favoring diplomates of the Board, and even the lay public is becoming aware of the implications of certification. That the certificate itself is gradually gaining prestige, there can be no doubt.



## Original Communications

### AN EVALUATION OF ANDROGENIC THERAPY IN GYNECOLOGIC PRACTICE\*

JOHN W. HUFFMAN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School and the Gynecological Service of Passavant Memorial Hospital)

#### PART I. A REVIEW OF EXPERIMENTAL WORK WITH THE ANDROGENS IN RELATION TO THERAPY

MANY clinical and experimental reports have recently appeared regarding the action of the male sex hormone upon the female genitalia. During the past three years an attempt has been made to analyze the effects of androgens when administered to laboratory animals and to human beings. It is proposed to correlate the results of these efforts with those previously recorded in the literature. Although the outcome of experiments in the use of male sex hormone will be reported herewith, a chief motive in preparing this paper has been a desire to clarify the use of androgens in gynecologic practice.

The experimental work upon which the use of the male sex hormone in gynecology is based will be considered in Part I of this review. Clinical results obtained with androgen therapy will be reviewed in Part II.

#### EFFECTS OF ANDROGENS UPON THE FEMALE GENITALIA AND THE HYPOPHYSIS

Following the work of Ihrke and D'Amour<sup>2</sup> who were able to inhibit the sexual activity of female animals by the injection of extracts of bull testes, Moore and Price<sup>3</sup> advanced the hypothesis that this inhibition was the result of a pituitary inactivation. This has been substantiated by the work of Hamilton and his co-worker.<sup>4</sup> Their investigations have shown that the pituitary glands of androgen-injected rats, when transplanted into immature females of the same species, have a decreased gonadotropic activity. They<sup>5</sup> have also demonstrated histologic changes in the hypophyses of female rats after repeated injections of testosterone propionate given over a prolonged period. A decrease in the number and a degranulation of the basophilic elements were evident in the pituitary glands of the animals which they injected with male sex hormone.

During the course of several recent investigations, examinations have been made of the pituitary glands of adult female rabbits, and of immature, and mature female rats which had received frequent injections of testosterone propionate<sup>†</sup> over considerable periods of time. These

\*Presented at a meeting of the Chicago Gynecological Society, May 17, 1940.

†Testosterone propionate in the form of Perandren was very kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for all of the author's investigations reported herewith.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

observations confirm the published reports of Hamilton and Wolfe. In addition, we have been interested in the work of Friedgood<sup>6</sup> who observed large acidophilic granules appearing in the hypophyses of female rabbits shortly after coitus. In five androgen-injected rabbits, similar phenomena were not discovered although the animals apparently had mated. Friedgood's findings were substantiated in 3 of 5 normal animals.

While unquestioned proof of a direct inhibitory effect produced by androgens on the pituitary of the human female has not been reported, the observation of Salmon<sup>7</sup> is of interest; in one castrated woman he demonstrated a precipitate decrease in the urinary gonadotropic level after androgenic therapy. Nathanson and Towne<sup>23</sup> also observed a fall in urinary female sex hormone levels after the administration of testosterone to female castrates.

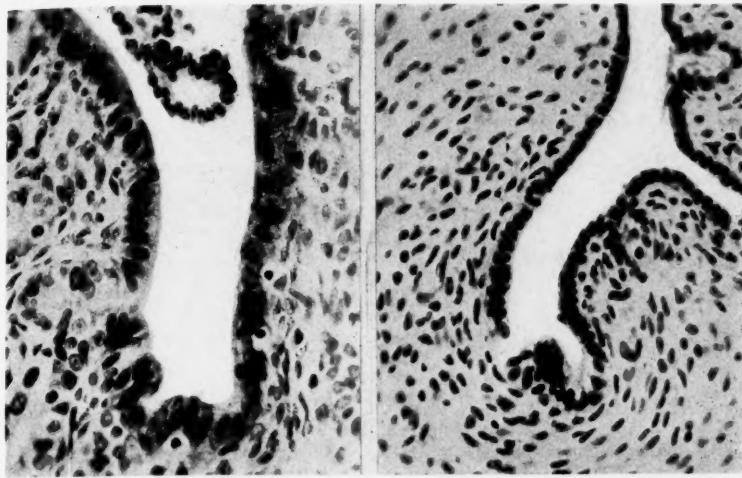
If there is a notable inhibition of the pituitary gland as a result of the administration of androgens, we should expect to find associated alterations in the genitalia.

The presence of cyclic changes in vaginal smears from the rat makes it simple to observe genital activity in this species. Smears from a group of adult female animals in our colony were examined until the fact that they had regular cycles could be established. They were then given daily injections of testosterone propionate. After a few days all smears showed diestrus, and the animals remained in that state as long as the injections were continued. After the injections were discontinued, the cycles returned to normal. Similar results have been recorded by Brownman<sup>8</sup> and by Robson.<sup>9, 59</sup> Robson also reported<sup>13</sup> that testosterone inhibits the ability of estrogens to induce vaginal cornification in the castrated mouse. Papanicolaou<sup>10-12, 61</sup> has duplicated these animal experimental findings in the human female. Vaginal smears taken from a number of women in a series which will be reported in Part II indicated a marked lowering of estrogenic activity while the patients were receiving testosterone propionate. Smears from these patients revealed an absence of cornified vaginal epithelium; they consisted only of small, darkly staining, mucified epithelial cells with comparatively large nuclei.

Conflicting reports have appeared in the literature regarding the effect of androgens on the uterus of experimental animals. Korenchevsky and others<sup>14-18, 66</sup> have noted that uterine hypertrophy and ovarian activity<sup>19, 20, 82-88</sup> have appeared in the rat following the administration of male sex hormone. Williams and his co-workers<sup>21</sup> state, however, that testosterone tends to decrease the endometrial hyperplasia produced in castrated guinea pigs by estrogens. Engle and Smith<sup>22</sup> found that the bleeding following the use of estrogens in the monkey could be inhibited by testosterone propionate. Leonard, Sager and Hamilton<sup>54</sup> observed that testosterone propionate decreased the estrus rhythm of the rabbit uterus. That androgens will delay menstruation in monkeys was demonstrated by Zuckerman<sup>35</sup> and also by Hartman.<sup>36</sup> In every instance in which we administered male sex hormone to adult rats and rabbits over long periods of time and in amounts comparable to those given therapeutically to women, the uterus was found to be inactive with a thin endometrium and small glands. At no time were phenomena suggesting estrogenic or progestational changes observed (Fig. 1).

Geist, Salmon and Gaines<sup>44, 65</sup> demonstrated atrophy of the human endometrium in suction curettings obtained after injecting patients with testosterone propionate.

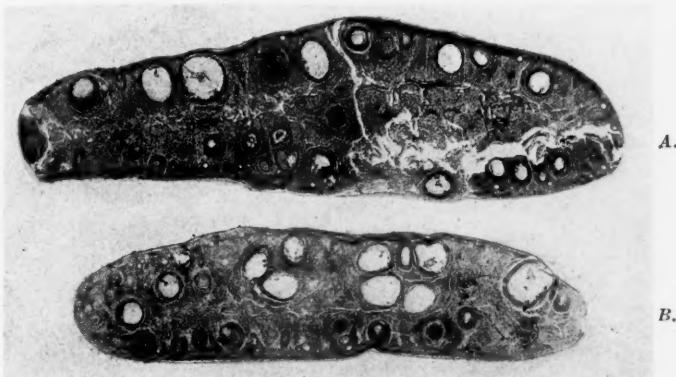
In my cases similar effects were obtained. Most of the patients in this series suffered from functional uterine bleeding; several were proved to have endometrial hyperplasia as shown by curettings. In each instance in which the endometrium was examined histologically



A.

B.

Fig. 1.—*A*, Photomicrograph of a portion of the endometrium in a section from the cornu of the uterus of a normal isolated adult female rabbit. *B*, Photomicrograph of a similar portion of the opposite uterine cornu of the same animal after it had received 2.5 mg. of testosterone propionate every other day for thirty-six days. Thinning of the endometrium and lessening of cellular activity in the latter is evident. Both photomicrographs  $\times 660$ .



A.

B.

Fig. 2.—*A*, Photograph of a longitudinal section through the right ovary of a normal adult rabbit. *B*, Similar section through the left ovary removed after the animal had received 2.5 mg. of testosterone propionate every other day for thirty-six days. The absence of any notable difference in the two ovaries is to be noted. Both photographs  $\times 11$ .

after patients had received 250 mg. or more of testosterone propionate, it was observed that the endometrial glands were small and far apart. They were usually lined by columnar epithelium with basal nuclei. This is a picture of inactivity rather than a resemblance of senile atrophy (Fig. 6).

The ovaries from mature animals injected with androgenic substance show little gross or histologic deviation from the normal. There is an absence of corpora hemorrhagica or recent corpora lutea after the injections have been given for a number of days. Atretic follicles are present. The primordial follicles appear unchanged by administration of the male sex hormone. This is in accord with published reports that follicular and luteinizing changes in the ovaries of laboratory animals are prevented by injections of testosterone propionate<sup>77</sup> (Fig. 2). Similar observations have been made in the human being. They will be described in more detail later in this report.

The external genitalia of the mouse,<sup>81</sup> the rat,<sup>62</sup> and the rabbit exhibit marked responses to repeated injections of massive doses of testosterone propionate. In the adult female rat the phallus becomes notably hypertrophied and in several instances in our animals an os priapi was demonstrable histologically (Fig. 3). In the rabbit after the injection of large amounts of androgenic material, the



A.

B.

Fig. 3.—A, Photomicrograph of a section through the phallus of a normal adult female rat. B, Similar section through the phallus of a female litter mate which had received 3 mg. of testosterone propionate daily for twenty-one days. The marked hypertrophy in the latter with the appearance of an os priapi beneath the urethra is evident. Both photomicrographs  $\times 10$ .

penile structure at the upper margin of the vaginal orifice developed to a size comparable to the penis of the male (Fig. 4). Hamilton and Wolfe<sup>57</sup> have noted the development of a prostatic type of paraurethral gland in female rats after administration of male sex hormone. These changes seem to develop in proportion to the amount of the hormone administered. In those animals not destroyed after the injections were discontinued, the androgenic manifestations gradually subsided, and the genitalia returned to normal. In a certain percentage of women, comparable masculinizing changes develop, as reported by Greenhill and Freed<sup>24</sup> and by Varangot.<sup>1</sup> Similar results have been observed in some of the cases followed in the dispensary at Northwestern University Medical School and will be mentioned in more detail later.

Numerous reports in the literature state that luteinizing and cystic changes in the ovaries,<sup>25, 71, 82</sup> stimulation of the endometrium,<sup>14-16, 29, 75</sup> and proliferation of the mammary gland,<sup>28, 51, 52, 55, 56</sup> occur after androgenic therapy. Most of these experiments have been conducted with immature rats as the experimental animals. The doses of the hormone used were greater than any which would compare with the amounts administered in clinical investigations. A relatively

small number of large injections were given. I have seen bizarre effects in immature rats when unusually large doses of testosterone propionate were repeated over a short period of time. Without further study, I am not satisfied that these phenomena are estrogen-like or stimulative. Mazer and Mazer,<sup>31</sup> however, found that prolonged androgenic treatment in the rat resulted in a decrease in

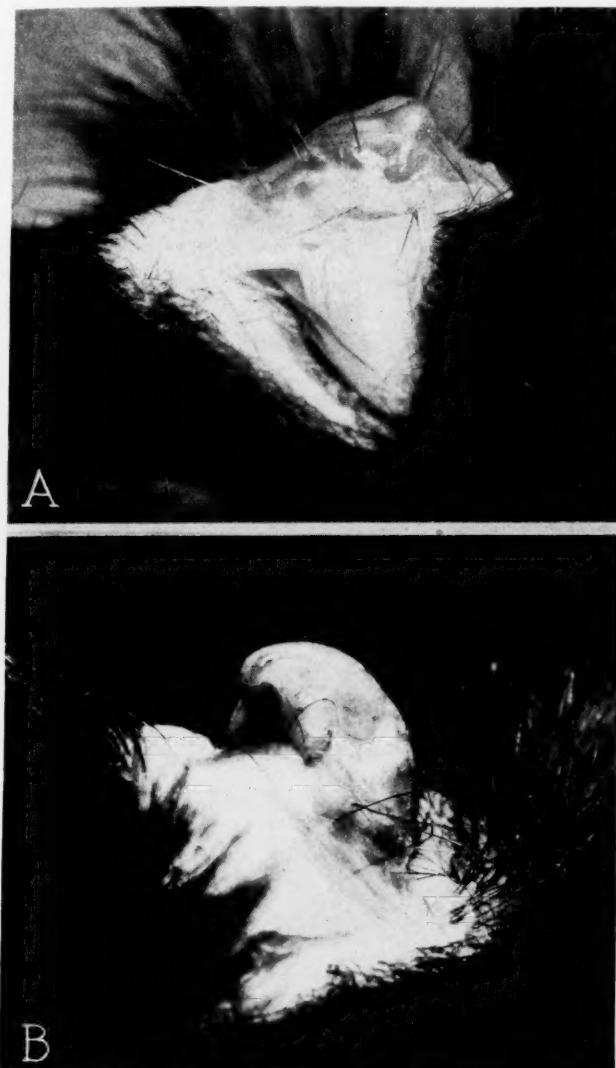


Fig. 4.—*A*, The external genitalia of an adult female rabbit. The vaginal aperture and slight clitoridal prominence are to be observed. *B*, Photograph of the external genitalia of a female litter mate after it had received 10 mg. of testosterone propionate daily for fourteen days. The great enlargement of the clitoris is evident. Camera distance for both photographs is the same.

the weights of the ovaries and uteri. They felt, therefore, that the duration of treatment is an important factor in the response of the genitalia to testosterone propionate. Hertz and Meyer<sup>60</sup> have demonstrated the effectiveness of small doses of male sex hormone. The biphasic action of the androgens as an explanation of their apparent gonadotropic effect, as suggested by Freed, Greenhill, and

Soskin<sup>32</sup> is of great interest, as is also the suggestion of Nelson and Gallagher,<sup>25</sup> and of Mazer and Mazer that coincident with the beginning of pituitary inhibition there is a pouring out of stored gonadotropic material from the hypophysis. Either of these hypotheses might explain the apparent stimulating action of testosterone upon the genitalia occasionally observed.

#### THE OVARIAN RESPONSE TO GONADOTROPIC SUBSTANCE FOLLOWING PROLONGED ADMINISTRATION OF TESTOSTERONE PROPIONATE

The effect of testosterone propionate in inhibiting the cyclic phenomena in the female genitalia<sup>35, 36</sup> and in producing those changes just described suggested the importance of conducting additional investigations as to its mode of action on the female genitalia. It seemed worth while to determine whether the action of this androgen was a direct one upon the ovary, or whether it was secondary to hypophyseal inhibition as strongly suggested by the work of Hamilton and of others.<sup>37, 63</sup> In previously reported experiments<sup>38</sup> isolated adult female rabbits were first proved able to respond to gonadotropic substance. Following this they were given injections of testosterone propionate over a period of several weeks. The presence of corpora hemorrhagica and recent corpora lutea, as a response to a second dose of gonadotropic material administered with the last injection of testosterone propionate, was strong evidence that androgens do not inhibit ovarian activity per se. Their action in stopping the genital cycle was, therefore, apparently an hypophyseal effect.

#### THE EFFECT OF TESTOSTERONE PROPIONATE UPON FEMALE REPRODUCTION\*

The preceding investigations indicated that the androgens were potent agents in temporarily changing those cyclic factors in the mammalian female which have to do with reproduction. All of the experimental work thus far had pointed to the fact that the androgenic effect on the sexual mechanism was maintained only a short time after the injections were stopped. So far as was known no one had applied the critical test of attempted reproduction following prolonged androgenic therapy although the results obtained by Sciphiades<sup>26</sup> and by Magistris<sup>67</sup> were suggestive.

Adult female rats received daily injections of testosterone propionate until it was shown by vaginal smears that they were in diestrus. They were then caged with healthy males. The daily injections of testosterone propionate were continued. As long as this procedure was followed, estrus did not occur and no young were born. The males were then withdrawn and the injections stopped; estrus recurred. After regularity of the sexual cycle was proved, the animals were again mated. Almost invariably pregnancy occurred; normal grossly healthy young were delivered.

#### EFFECT OF TESTOSTERONE PROPIONATE UPON LACTATION\*

Reports in the literature have been made stating that in experimental nonlactating animals fibrosis occurs in the stroma of the mammary

\*This item will be more fully detailed in subsequent accounts.

gland after injections of synthetic male hormone.<sup>39, 79</sup> Folley and Kon<sup>64</sup> and others<sup>80</sup> state that androgens will inhibit lactation. Robson<sup>50</sup> and Burrows<sup>74</sup> have produced evidence to show that young rats die when their mothers are injected with androgenic material. Kurzrok and O'Connell<sup>40</sup> and others<sup>70, 72, 73</sup> have conducted clinical investigations which indicate that the administration of testosterone propionate to women in the puerperium decreased breast engorgement and pain. Numerous papers have been written regarding the efficacy of the male sex hormone in the treatment of mastalgia and mastitis.<sup>27, 30, 68, 69</sup> It was therefore suggested that androgens tend to decrease breast activity. It seemed desirable to determine what effect, if any, the male hormone would have upon the histology of the breast if the young were permitted to suckle during the time the mother was receiving androgenic substance. Normal female rats which had borne healthy litters were selected. Injections of testosterone propionate were begun within twenty-four hours of delivery and continued daily. The appearance of the breasts and the state of nutrition of the offspring were observed. Histologic studies of the breast tissue were made at varying intervals of time in the puerperium. In every instance in which the mother received testosterone propionate the young died within sixteen days of birth, evidently of malnutrition. Breast tissue removed at the time of the death of the litter showed absence of lactation. Controls, injected with comparable amounts of the vehicle (sesame oil), reared healthy litters. Breast tissue removed from the controls demonstrated normal lactation.

THE REPRODUCTIVE ABILITY OF THE OFFSPRING OF FEMALE ANIMALS  
PREVIOUSLY TREATED WITH TESTOSTERONE PROPIONATE\*

Ivy and Greene<sup>41</sup> have shown that injections of androgens in pregnant rats will result in grave abnormalities in the genitalia of the offspring. We<sup>†</sup> have shown that females who received male sex hormone could bear grossly normal young following cessation of the injections. These progeny were followed during development. Body growth appeared normal. Records were kept of each individual and matings were made between males and females born of mothers which had received testosterone propionate prior to their pregnancies. In every instance healthy litters were obtained from this second generation. The females suckled their young normally, and the progeny developed in a satisfactory fashion.

SUMMARY

Although there is not a unanimity of opinion regarding the effects of androgenic substances when administered to female mammals, it would appear that most of the experimental work presented to date indicates the following changes develop in laboratory animals after the administration of male sex hormone: (1) A decrease in the gonadotropic activity of the hypophysis, (2) cessation of genital cyclic phenomena

\*This item, herewith presented as a preliminary report, will be more fully detailed in subsequent accounts.

†Experiments on this phase of the work were conducted with Florence K. Huffman.

as a result of pituitary rather than of ovarian inactivation, (3) inhibition of lactation, (4) the occurrence of temporary masculinizing characteristics after the administration of large doses of the androgens, (5) recurrence of all genital physiologic processes including normal reproduction after the administration of the androgenic substance is discontinued.

#### PART II. A CRITICAL REVIEW OF CLINICAL RESULTS OBTAINED WITH ANDROGENIC THERAPY

In Part I of this review the experimental studies upon which the use of male sex hormone in gynecologic practice is based were discussed. Part II, presented herewith, is a summary of clinical results obtained with androgen therapy in gynecology, with a review of the corollary literature.

##### USE OF MALE SEX HORMONE IN CASES OF FUNCTIONAL UTERINE BLEEDING

During the past two and one-half years records have been kept of 22 women with a clinical diagnosis of functional bleeding who received androgenic therapy either alone or in combination with other non-surgical treatment. In this group it was possible, without exception, to inhibit functional flow and menstruation when 25 mg. of testosterone propionate in the form of perandren (Ciba) were administered every other day. It usually required 10 to 15 injections (a total of 250 to 450 mg.) to stop the bleeding. Smaller doses (10 mg. twice weekly) when administered to women complaining of heavy or somewhat prolonged menstruation usually decreased the amount of bleeding and shortened the duration of flow but did not inhibit the cycle. When using the large (25 mg.) dosages, it has been customary to give not more than 2 or 3 injections after the flow has ceased. The longest period of amenorrhea following one series of injections has been one hundred and three days.

Of particular interest in this group of 22 women are three patients who have been under observation for two years or longer. Each one of these three, prior to the beginning of treatment, had bled for more than sixty days and had lost enough blood to develop marked secondary anemia. Curettage in all three had demonstrated endometrial hyperplasia. One patient, in fact, had been curedtted six times between the ages of sixteen and twenty-four years. Two of them had received large amounts of anterior pituitary-like substance without benefit. All three were comely young women under the age of 35 who met the public daily and whose livelihood depended upon their continuing at work. They were all exceedingly anxious to preserve whatever childbearing ability they possessed. Androgenic therapy was begun in the form of 25 mg. of testosterone propionate injected intramuscularly every other day. In each instance the bleeding continued unabated for ten to fourteen days, after which the flow gradually ceased and stopped entirely on the twelfth to the eighteenth day. Three additional injections were given. The subsequent amenorrhea persisted for 68, 74, and 93 days, re-

spectively. In each case this was followed by a scanty flow of from one to three days. Three to five weeks later a slightly heavier period occurred. One month following this last flow two of the women menstruated normally, and the third had a recurrence of persistent functional bleeding requiring the repetition of a series of injections. The two who had menstruated normally subsequently noted a gradual increase in the duration and heaviness of their menses and received testosterone propionate in the dosages previously described. Series of injections have had to be repeated in all three approximately every four to six months. At no time have their blood counts fallen below normal limits, nor have they been prevented from working because of excessive flow. The other patients in this series, who have been under observation less than two years and received larger dosages, have responded in a somewhat similar manner, with the exception of two whose menstrual cycles returned to normal and have remained so for six months. No notable masculinizing symptoms have occurred in this group, except for occasional enlargement of the clitoris toward the end of the series of injections. One woman who possessed rather marked facial hair noted that it became darker; upon cessation of the treatment this disappeared.

Male sex hormone has been used more for the treatment of functional uterine bleeding than for any other gynecologic condition.

Gaines, Salmon and Geist<sup>65</sup> pointed out that 25 to 100 mg. of testosterone propionate injected intramuscularly every two or three days until a total of 175 to 800 mg. was given would result in a disappearance of the secretory phase of the endometrium and in an inhibition of endometrial proliferation. This they suggested was the result of suppression of the gonadotropic activity of the hypophysis. Shortly after this report, they<sup>44</sup> published a record of 25 women suffering from functional uterine bleeding. Twenty-four of the women were relieved by the use of testosterone propionate in doses of 300 to 1,000 mg. per month. Foss<sup>33</sup> not only inhibited uterine flow but produced an atrophy of the endometrium following the injection of 300 to 2,000 mg. of male sex hormone to each of 16 patients. Loeser<sup>45</sup> recommended a dosage of 50 mg. of testosterone propionate injected every other day with an average total monthly dosage of 500 mg. for menorrhagia. He found that with these amounts atrophy of the endometrium, inhibition of uterine bleeding, and decrease in the size of uterine fibromyomas occurred. Mazer and Mazer,<sup>42</sup> Greenhill and Freed,<sup>58</sup> and others have reported the effective control of excessive uterine bleeding by the injection of male sex hormones. Rubenstein<sup>77</sup> reports one case in which the bleeding ceased after the administration of 5 mg. of testosterone propionate injected twice weekly. Sturgis and his co-workers<sup>78</sup> found that the minimum dosage required to lessen the flow in cases of metromenorrhagia was 10 to 30 mg. and that the total amount required to stop the flow was 10 to 120 mg. These are, by far, the smallest dosages recommended. Mazer and Mazer, Greenhill and Freed, Geist and his associates have all apparently arrived at about the same dosage as that used in the patients described in the preceding paragraphs, i.e., 250 to 500 mg. monthly, given in divided doses throughout the month. Salmon and his co-workers<sup>53</sup> noted that masculinization tended to develop when more than 500 mg. of testosterone propionate were administered, and they feel that this amount should be considered a human "threshold." Many investigators who have given androgens a clinical trial would undoubtedly prefer not to give more than 350 to 400 mg. in any one month. Most functional bleeding cases will respond to 25 mg. given intramuscularly every other day for a total of 12 to 16 injections (300 to 400 mg.). Loeser<sup>89</sup> has recently reported the satisfactory use of pellets of androgenic substance planted subcutaneously in women suffering from functional uterine bleeding and mastopathies.

## THE USE OF MALE SEX HORMONE IN CASES OF DYSMENORRHEA, AFTER-PAINS, AND PREMENSTRUAL MOLIMEN

In 1937, Demarest and Capitain<sup>30</sup> reported excellent results in the treatment of dysmenorrhea with injections of testosterone. Salmon, Geist, and Walters<sup>31</sup> administered testosterone propionate in dosages of 10 to 50 mg. to 30 women who complained of severe dysmenorrhea. The injections were given three times a week during the cycle. Good results were obtained in 26 of 30 patients. They felt that 250 to 300 mg. of testosterone propionate, given in divided doses through one menstrual cycle, would give relief to most of their patients. If discomfort recurred the next month, they repeated a series of injections but reduced the dosage to one-half that previously given. Greenhill and Freed<sup>32, 33</sup> observed that one-half of their cases of dysmenorrhea, treated with 25 to 50 mg. of testosterone propionate given three times a week for each of the two weeks prior to menstruation, continued to have benefit one year after discontinuance of the therapy. They feel that male sex hormone in amounts less than required to stop uterine flow will relieve dysmenorrhea. Rubenstein and Abarbanel<sup>49</sup> found that most of their cases of essential dysmenorrhea responded satisfactorily to male sex hormone. They explained that this resulted from a lowering of estrogenic and gonadotropic levels and a consequent decrease in painful uterine contractions. Recently Abarbanel<sup>51</sup> has found the percutaneous route satisfactory for administering androgenic substance to patients with painful menses. He prefers to use testosterone propionate in sesame oil rather than an ointment.

Premenstrual tension and major menstrual molimen were relieved by small doses of testosterone according to Greenblatt.<sup>50</sup> In several patients who complained of severe molimen he was able to give complete comfort and also to relieve associated excessive cyclic bleeding when he administered 10 to 50 mg. of testosterone propionate per month. Abarbanel and Rubenstein<sup>49</sup> have made similar observations. Abarbanel has also<sup>50</sup> reported that in 82 per cent of 49 patients afterpains were relieved by the injection of 10 mg. of testosterone propionate. No afterpains occurred in 88 of 100 women who received 10 mg. of androgenic substance given prophylactically at or near the time of delivery.

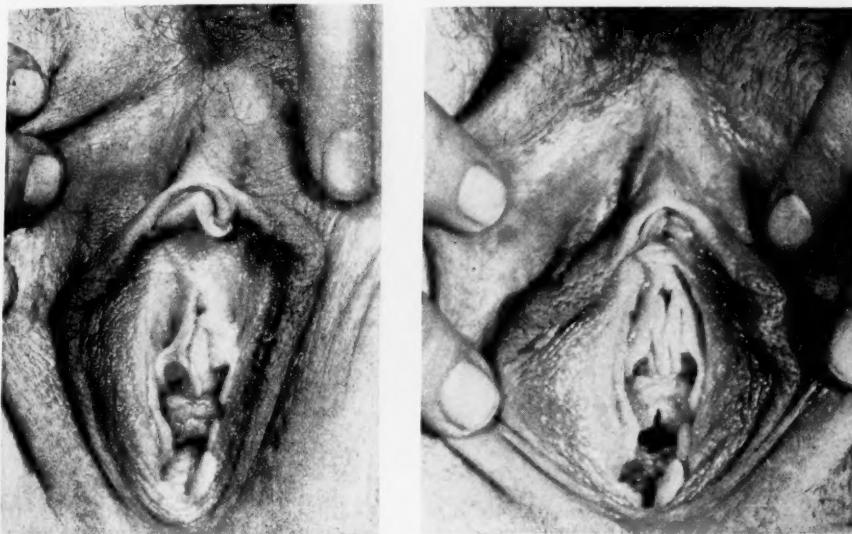
## USE OF MALE SEX HORMONE IN CASES OF FEMALE MENOPAUSAL DISTURBANCES

Mocquot and Moricard<sup>47</sup> first reported the use of androgenic substances in the treatment of climacteric disturbances following bilateral ovariectomy. Margeil and Zwilling<sup>48</sup> found male sex hormone effective in the management of the natural menopause. These authors used very small doses without uniform results. Salmon, in 1937, reported cessation of menopausal symptoms in one female castrate following the administration of 400 mg. of testosterone propionate in divided doses. Binberg, Kurzrok and Livingston<sup>34</sup> noted the disappearance of severe climacteric symptoms which had followed castration, x-ray, and radium when they injected 10 mg. of testosterone propionate twice weekly. Subsequently they reported<sup>46</sup> a series of 21 patients who were relieved of menopausal headaches, flushes, and sweats by the injection of 30 to 50 mg. of testosterone propionate weekly. They began their treatment with 25 mg. twice a week, later reducing the dosage to 30 or 40 mg. given weekly. There were no failures in their cases, and they were able to administer testosterone to some women who could not tolerate estrogens. They feel there is a definite place for androgenic therapy in the management of the menopause.

## USE OF MALE SEX HORMONE FOR THE INHIBITION OF LACTATION, IN CASES OF BREAST ENGORGEMENT, AND IN MASTOPATHIES

Considerable experimental evidence exists to indicate that androgens should decrease mammary gland activity. Clinical experiences bear this out.

Demarest and Capitain<sup>30</sup> were the first to report satisfactory results when androgenic substances were administered to women complaining of premenstrual breast engorgement and mastalgias. They used small dosages (5 mg.) and did not have uniform results, probably because of the small amount of the hormone administered. Kurzrok and O'Connell<sup>40</sup> successfully inhibited lactation in 19 of 21 puerperal women when 25 mg. of testosterone propionate were injected intramuscularly twice daily for one to three days. None of these patients had notable engorgement on this regimen. Abarbanel<sup>70</sup> was able to relieve post-partum breast engorgement in 44 of 50 patients by the intramuscular injection of 5 mg. of testosterone propionate; occasionally it was necessary to repeat this dose in one hour. More recently Siegler and Silverstein<sup>72</sup> and Binberg, Kurzrok and Klor<sup>73</sup> have reported inhibition of lactation following the administration of androgenic substances. Siegler and Silverstein found that injections of from



A.

B.

Fig. 5.—A, The external genitalia of a patient under treatment for functional uterine bleeding who had received 350 mg. of testosterone propionate given over a period of several weeks, preceding the taking of this photograph. Note the increase in the length and diameter of the clitoris with the massive enlargement of the glans. B, One month after the last injection of testosterone. Note that the clitoris is normal in appearance and that the temporary hypertrophy seen in A has disappeared. The camera distance for both photographs is identical.

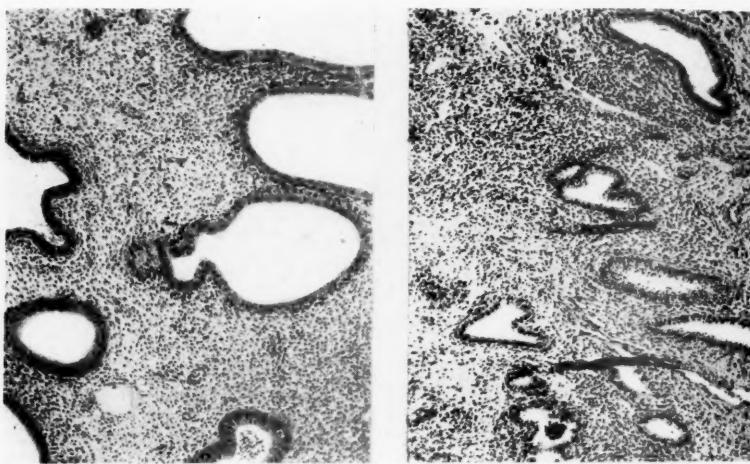
3 to 10 mg. of testosterone propionate were effective in 94 per cent of their patients. Binberg and his associates injected 120 to 150 mg. of testosterone propionate intramuscularly in divided doses on the day of delivery. They record that 49 of their 56 patients did not lactate as a result of this procedure.

#### CORRELATION OF LABORATORY AND CLINICAL FINDINGS

In order to correlate, if possible, the laboratory findings with the clinical investigations, changes were sought for in my patients analogous to those noted in experimental animals. The discovery that comparable phenomena (as far as the investigations could be extended) did occur is of great interest.

The women who received the largest amounts of testosterone (400 mg. or more) over the longest period of time tended to develop definite hypertrophy of the clitoris (Fig. 5). On cessation of each series of

injections, this hypertrophy disappeared. In each instance in which vaginal smears were taken after 250 mg. of male sex hormone had been given, there was an almost complete absence of any demonstrable estrogenic activity. In those instances in which endometrial hyperplasia had been observed in curettings obtained prior to treatment, it was noted that, after androgenic therapy, the tissue removed by suction curettage showed no hyperplasia; there were, instead, comparatively few, small, inactive glands (Fig. 6). While none of the patients who have been followed in this series have attempted pregnancy, Mazer and Mazer<sup>42</sup> report four women from their group of 38 who had normal gestations after androgenic therapy.



A.

B.

Fig. 6.—A, Photomicrograph of uterine scrapings from a patient with typical endometrial hyperplasia. She had been bleeding for seventy-two days. B, Endometrial suction curetting from the same patient after she had received 350 mg. of testosterone propionate. Both photomicrographs  $\times 132$ .

In one patient in whom the diagnosis of submucous fibromyomas was made and who had bled constantly for many weeks (entering the hospital with a hemoglobin of 4.5 Gm. and an erythrocyte count of 2,500,000 per c.m.m.), androgenic therapy was given to inhibit, if possible, further flow during the days in which preparation for operation was being made. She received 25 mg. of testosterone propionate daily for fourteen days. It is interesting to relate that no bleeding occurred during the two weeks preceding surgery and that the transfused blood given her was conserved so that at the time of her hysterectomy she had essentially normal blood counts. Some hypertrophy of the clitoris and an inactive vaginal smear were noted the day before operation. It was felt that an unusual opportunity presented itself for observation of the gross and microscopic appearance of the genitalia in this patient who had received an average amount of androgenic therapy. At operation it was noted that the ovaries were somewhat shrunken, pale, with no gross follicles and no evident corpora lutea. The uterus, although

enlarged by the tumor, was pale. The Fallopian tubes appeared normal. There was no suggestion of pelvic engorgement or increased vascularity. The opened uterus showed a thin endometrium, not only in the region of the tumor but also far removed from it. Microscopic examination of the endometrium gave a more complete picture than had been possible



Fig. 7.—Photomicrograph of a section of the uterus showing the endometrium obtained from a patient who had had a hysterectomy because of fibromyomas. She had received 325 mg. of testosterone propionate during the fourteen days preceding operation.  $\times 140$ .

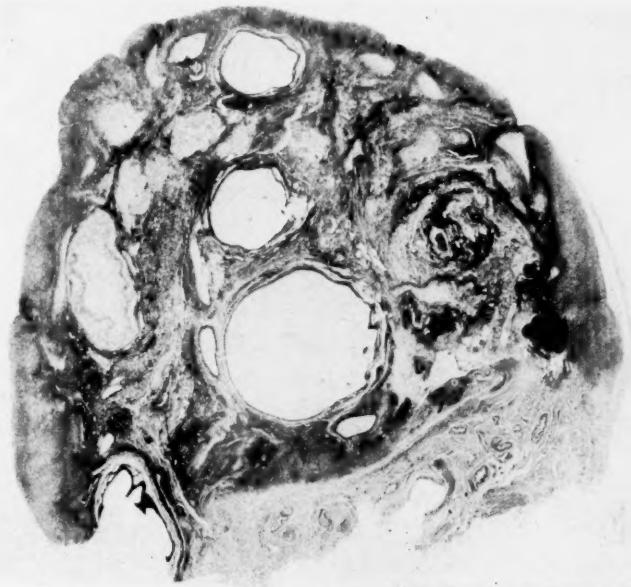


Fig. 8.—Section through the ovary of a patient who had received 325 mg. of testosterone propionate during the fourteen days preceding operation. The absence of recent follicles or young corpora lutea will be noted.  $\times 5$ .

with curettings obtained in previous studies. There was thinning of the endometrium with very few glands in a nonsecretory state. These glands were lined by a single layer of cells with small basal nuclei. This is not the picture commonly seen in senile atrophy. It is rather one of inactivity (Fig. 7).

Section through an ovary disclosed small atretic follicles and no young corpora lutea (Fig. 8). The follicles were lined with small shrunken granulosa cells. There was a thin cortex containing occasional primordial follicles but no ripening or maturing Graafian follicles were found (Fig. 9). The granulosa cell layers of all follicles

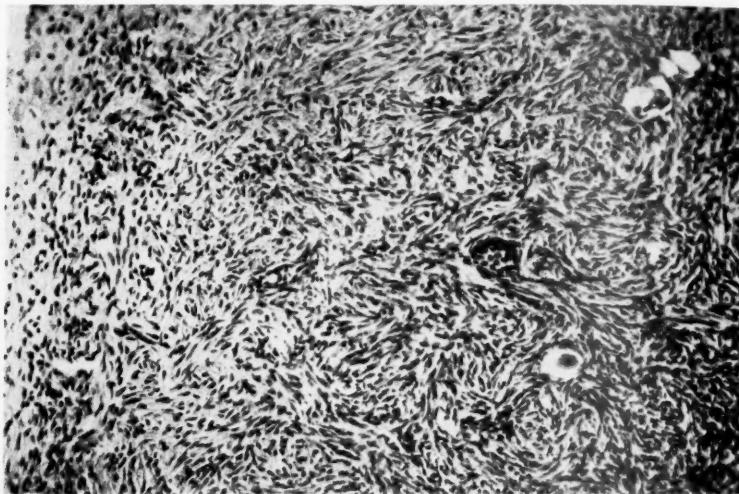


Fig. 9.—Photomicrograph of a portion of the cortex of the ovary seen in Fig. 8. Note the occasional apparently normal primordial follicles.  $\times 130$ .

were thin, with pale shrunken cells which showed no suggestion of activity. The medullary portion of the ovary was normal. In this patient the findings noted in the laboratory animals have been duplicated in the human being in a most satisfactory manner.

\* \* \* \* \*

With this review of the laboratory and clinical investigations as a foundation let us attempt to evaluate androgenic therapy as to its advantages, disadvantages, indications, and contraindications.

#### ADVANTAGES AND DISADVANTAGES OF ANDROGENIC THERAPY IN GYNECOLOGY

The treatment of functional uterine bleeding with androgens has certain advantages. It is ambulatory which to many patients is a great convenience. It is perhaps the most effective of the nonsurgical measures available in the treatment of functional flow. There is no operative risk attached to its use. More important, so far as can be determined, there is a preservation of whatever reproductive ability the patient possesses. In event of subsequent pregnancies in a patient who

has received testosterone, there is every reason to believe that normal offspring will be born and that these offspring will have normal reproductive powers. If androgenic therapy proves worthwhile in dysmenorrhea, afterpains, and menstrual molimen, the value of having a simple, innocuous, and effective treatment for these conditions requires no comment. The advantages resulting from the administration of male sex hormone in the routine treatment of menopausal disturbances seems somewhat questionable at this time.

Some disadvantages exist in the use of male sex hormone in women. First and most important is the very real danger of producing masculinizing phenomena when such materials are given in large doses to women who already possess android characteristics. The fact that these changes are temporary does not wholly overcome this disadvantage. A second disadvantage is that the treatment of functional uterine bleeding in many cases is not truly curative. In most instances, the flow is inhibited for many weeks, but there is a distinct tendency for the excessive bleeding to recur after a period of months has passed.

#### INDICATIONS AND CONTRAINDICATIONS TO THE USE OF ANDROGENIC THERAPY IN GYNECOLOGY

On the basis of the many reports in the literature<sup>33, 43-45, 76-78</sup> and after having administered testosterone propionate to 22 women for the treatment of functional uterine bleeding, it is felt that there is a definite, although perhaps limited, place for androgenic therapy in the management of this disorder. It affords an almost certain means of inhibiting functional uterine flow. Its use appears indicated in women who do not have major pelvic pathology and in whom it is desirable to avoid extensive surgical procedures. This is particularly true of younger women in the childbearing years who are desirous of preserving their fecundity and of older women in whom the appearance of the climacteric within a relatively short time may be expected to put an end to excessive bleeding. There is no doubt that, of the many nonsurgical procedures now in use for functional menorrhagia, androgenic therapy may be expected to yield the most certain results. On a theoretical basis, inhibition of the menses by male sex hormone should be especially advantageous to women with pulmonary tuberculosis who suffer from an exacerbation of their chest pathology each time they menstruate.

If the work of Kurzrok and his associates is any criterion, androgenic therapy should be of value in premenstrual breast pain and in painful breasts during the early puerperium. While my experience in the use of testosterone propionate in the treatment of mastalgias and puerperal engorgement has been limited, it has been found efficacious in the few instances in which it was employed. It would appear that approximately one-half of the amount of testosterone used to inhibit uterine bleeding is effective in mastopathies and that 100 to 150 mg. will prevent post-partum breast engorgement in most cases.

In view of the logical and satisfactory management of the menopause with estrogens, it seems out of place to use male sex hormone in the

treatment of disturbances of the climacteric as has been suggested by several authors.<sup>34, 46-48</sup> However, the fact that androgens are at times effective appears on the basis of published reports to be indubitable. That this effect is the result of a depression of the pituitary gland seems most probable. Best results appear to be obtained when 30 to 50 mg. of testosterone propionate are injected weekly. Despite the fact that estrogenic substance is the logical agent to employ in the menopause there may be an occasional instance in which androgens would be preferable. As Kurzrok has pointed out this would be true of individuals who are allergic to estrogenic materials. It also may be advisable to turn to androgens rather than to large doses of estrogens for the treatment of either natural or surgical menopause in patients who are known to have had extensive endometriotic implants or other new growths. In these types of cases, a desire to relieve menopausal symptoms and yet to avoid the stimulating effect of estrogens may make a trial with male sex hormone worth while.

Information obtained from the literature<sup>49, 53, 58</sup> suggests that androgenic therapy is indicated for the relief of primary (essential) dysmenorrhea where the discomfort is presumably due to painful uterine contractions in patients without demonstrable pelvic organic pathology to account for their distress. If further trial proves that testosterone will prevent menstrual molimen, its use in these often distressing cases will be strongly indicated.

Certain contraindications exist for the use of androgenic therapy in gynecologic practice. To attempt the management of uterine bleeding by any nonsurgical treatment, whether it be androgens, anterior pituitary-like preparations, or other therapy, without fully satisfying ourselves that organic abnormalities are absent, is hazardous. The presence of neoplasms, gross residues of infection, or retained products of gestation militate against the use of the male sex hormone. It is evident from the investigative work previously presented that definite masculinizing changes can occur when an excessive amount of testosterone propionate is administered. I feel very strongly that androgenic substances should not be given to a woman who presents notable android characteristics but that other means should be found for the management of her complaint. The presence of facial and pectoral hirsuties, especially on the upper lip and chin, or a heavy growth of coarse hair on the thighs, an unusually large clitoris or a deep voice are contraindications to androgenic therapy. Avoidance of the use of male sex hormone in such cases is advisable even though, almost without exception, the accentuation of masculinizing characteristics will disappear when the treatment is stopped.

The danger of overlooking organic pelvic disease in cases of uterine bleeding and dysmenorrhea, of serious breast pathology in mastalgias, and of systemic disorders associated with any of the conditions discussed should not go unmentioned. It need not be emphasized that there is always a considerable hazard of neglecting commonplace lesions when a new, effective, and at times startling therapeutic agent, such as androgenic therapy, is introduced.

## SUMMARY

Effects in 22 women who received androgenic therapy parallel those produced in laboratory animals by injections of testosterone propionate. In my cases, functional uterine bleeding was inhibited by the male sex hormone. In this group, no notable masculinizing changes developed, except occasional temporary hypertrophy of the clitoris. Three of these patients have been under observation for more than two years.

Testosterone propionate will bring about a cessation of genital activity in human beings as it has been observed to do in the adult female rabbits and rats. This effect is the result of pituitary rather than ovarian inactivation. The changes produced by the male sex hormone are temporary, with resumption of cyclic phenomena in the genitalia after administration is discontinued. When large doses of testosterone propionate (over 350 to 500 mg.) are injected over a considerable period of time, temporary masculinizing changes, especially hypertrophy of the clitoris, may appear. Inhibition of activity in the lactating breast after the administration of testosterone propionate has been observed clinically and has been demonstrated histologically in animals. Reports in the literature indicate that reproduction is possible and that normal young have been born to human beings who have received male sex hormone prior to their pregnancies.

There is considerable evidence to suggest that androgenic therapy has a place in the treatment of functional uterine bleeding, mastalgia and puerperal breast engorgement, and for the inhibition of lactation. Further investigation of its use in dysmenorrhea and the treatment of menstrual molimina seems indicated. The use of male sex hormone may, perhaps, be advantageously used in preference to the estrogens in certain selected instances of menopausal disturbances.

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#### DISCUSSION

DR. CARL R. MOORE.—About twenty years ago we believed strongly in the specificity of sex hormones, in particular in the reactions of specific sex structures to homologous hormones. But as potent tissue extracts and pure chemical hormones became available, we learned from experiment that opposite sex hormones did exert some type of effect. We can, therefore, consider the biologic reactions and therapeutic properties of male sex hormones for gynecologic disorders.

On logical grounds one may be somewhat puzzled to account for male hormone action in females. Thus, following male hormone administration, we may have suppression of estrus cycles, suppression of lactation, prolongation of gestation, or prevention of delivery and the prevention of menstrual bleeding. On the clinical side, we have reports that male hormone alleviates menopausal symptoms, aids in dysfunctional, as well as functional bleeding, and is efficacious in prevention of lactation.

In attempting to organize our conceptions, it appears that the mechanism of these results may fall into at least two main categories. The first of these has to do with action of the male hormone on the pituitary gland, while the second involves local or direct action on the end organs concerned. It is not always clear which of these may be involved, and indeed it is possible both are frequently involved.

It should be recalled first that the stimulus inciting activity in the sex glands is the pituitary body. At the same time the sex hormones produced exert an influence back upon the pituitary. This latter influence may be inhibitory in the direct sense and in some cases may be considered to introduce qualitatively different secretions on the part of the pituitary.

Suppose we look for a moment at the estrus cycle. If ovaries are removed, cycles are abolished; pituitary removal produces similar results; male hormone likewise suppresses them. In each case the lack of estrogenic substances is largely responsible. Cycles could also be abolished by injecting estrogens so far as pituitary suppression is concerned, but now by direct action the estrogens affect the uterus and vagina and bring them into a constant estrous condition. Male hormones likewise suppress the pituitary but do not stimulate the estrus response of the uterus. These aspects are of interest in the clinical treatment of menopausal symptoms. Presumably the direct causal agent of these symptoms is lack of the estrogenic substances to inhibit the pituitary. The excessive pituitary secretion should be suppressed by either male or female hormones. When estrogenic therapy is employed, it is to be expected that these substances will activate the uterus, and perhaps maintain an hypertrophied state. Male hormone will suppress the pituitary and not stimulate the uterus, and hence would appear ideal in some respects.

In a similar manner lactation is abolished by male hormone, apparently because of pituitary depression. Male hormone also decreases uterine motility; but whether this is due entirely to pituitary suppression, giving an indirect estrogenic suppression or is due to a direct action on uterine musculature is not certainly known. Certain phenomena of dysmenorrhea may be influenced by male hormone. It is not clear why it would be preferable to an estrogen in controlling pituitary activity for this condition, unless it be the fact that the addition of estrogens might further enhance a hypersensitive uterus.

Danger of injury to offspring conceived much later than androgenic treatment is unlikely, for hormone storage in the body does not occur and hormones as effective agents in modification of developing young act directly. On the other hand, although we do not know conditions in the human development, it is possible, as indicated by other experimentation, that serious developmental injuries to the reproductive system might follow treatments with male hormone during pregnancy.

In any treatment with sex hormones, androgens or estrogens, therefore, the action upon the pituitary, which typically reduces or abolishes ovarian secretions, as a secondary effect, constitutes one avenue of effectiveness, while the possible direct action on end organs or on general conditions constitutes another. This latter may not only involve reactions or responses on the part of the end organ in question but one must always consider such side effects as general heightening of masculine tendencies. These, especially if severe, may decidedly offset any advantageous responses on the part of the condition being treated.

DR. J. P. GREENHILL.—Clinically the male hormone has been found helpful to control or suppress abnormal uterine bleeding, to diminish the swelling and

pain which occurs in the breasts before the menses, to relieve some cases of dysmenorrhea and to prevent premenstrual tension in some cases. To control or suppress uterine bleeding, it is necessary to give between 300 and 500 mg. throughout an entire period, whereas for dysmenorrhea, premenstrual painful breasts, and premenstrual tension only about 150 mg. divided in six doses during the last two weeks of the menstrual cycle usually suffice. In most of the cases, the beneficial results are only temporary. In a few cases, however, the good results persist for a few months after two or three series of injections are given. Recently Dr. Freed and I have been using ammonium chloride to overcome premenstrual distress, and we have obtained most encouraging results with this simple, and inexpensive form of therapy.

I should like to emphasize the caution urged by Drs. Huffman and Moore. Large doses of testosterone propionate sometimes produce virilism effects, such as increased hair growth on the face, lowering of the pitch of the voice, and slight enlargement of the clitoris. In addition, many women gain weight and develop an acneform eruption. Fortunately all of these disagreeable effects disappear after the hormone is stopped.

**DR. HUFFMAN (closing).**—In a few instances, too few to report, we have noted satisfactory results in premenstrual breast pain after giving 25 mg. of testosterone propionate intramuscularly twice weekly for two weeks preceding menstruation. This has a temporary effect during the following menstrual period and must be repeated each month.

We have not been as fortunate as Dr. Greenhill in obtaining a permanent cure of functional uterine bleeding by means of injections of testosterone propionate. As months go on after a series of injections the patients tend to get a recurrence of prolonged flow. However, with the dosages we have been using (300 to 400 mg.) we have seen no masculinizing characteristics develop other than occasional hypertrophy of the clitoris. This hypertrophy disappeared entirely within two or three weeks after cessation of the therapy.

## CLINICAL EXPERIENCES WITH EQUINE GONADOTROPIC HORMONE

HENRY W. ERVING, M.D., CHRISTINE SEARS, M.D., AND JOHN ROCK, M.D., BROOKLINE, MASS.

(From the Sterility and Endocrine Clinic, Free Hospital for Women)

### INTRODUCTION

SINCE 1937 there have appeared 14 clinical reports on the use of equine gonadotropic hormone (E.G.H.). Hamblen,<sup>27, 45</sup> on two occasions, Frank,<sup>40</sup> and Watson, Smith and Kurzrok<sup>41</sup> are the only ones to report consistently negative results following administration of the hormone. The other 10 reports are by Bowes,<sup>39</sup> Davis and Koff,<sup>42</sup> Siegler and Fein,<sup>23</sup> Campbell and Sevringshaus,<sup>46, 51</sup> Kennedy and Shelton,<sup>47</sup> Hall,<sup>48</sup> Hawkinson,<sup>49</sup> Rubenstein,<sup>50</sup> and Gray.<sup>7</sup> Although they admit failures, they have all expressed either enthusiasm or optimism about this new gonadotropic hormone. We feel that none of these reports offers conclusive evidence of the value of equine gonadotropic hormone in stimulating ovulation in women, and that our own results bear out this contention.

### CLINICAL STUDY

In our study we used equine gonadotropic hormone, gonadin, prepared by the Cutter Laboratories, and in two cases supplemented this with anteron, prepared by the Schering Corporation.

Gonadin is dispensed in solution and each cubic centimeter contains 200 rat units. According to the Cutter Laboratories, a rat unit is "the amount of hormone which, when injected subcutaneously in a single dose into five immature female rats (twenty-one to twenty-three days of age), will produce an average of from 3 to 10 large follicles or corpora lutea at the time of autopsy ninety-six hours later, and half of which will not produce this average in another group of 5 rats similarly treated."

Anteron is dispensed in the form of dry stable pellets and its potency is expressed in international units. The Permanent Commission on Biological Standardization of the Health Organization of the League of Nations states that "the specific gonadotropic activity of 0.25 mg. (250 gammas) of the standard preparation shall be the international unit for recording the activities of all gonadotropic preparations of the serum of pregnant mares, but only of such."

New batches of gonadin were received frequently during this study to avoid the possibility of diminished potency, and the anteron was received a few days prior to its use.

The 48 cases in this study comprise 21 private and 27 clinic patients seen over periods ranging from six months to eight years. They fall roughly into three

groups although, of course, there is some overlapping. The largest group (Tables I and IA) consists of 26 patients with a chief complaint of sterility. The second group (Table II) of 6 patients complained of dysfunctional flowing, and the third group (Table III) of 16 patients complained of amenorrhea.

In 36 of the 48 cases, the diagnosis of ovulation or anovulation was made before treatment by endometrial biopsy, taken a few days prior to the onset of menstruation, and often repeated several times. Attempts at biopsy in 3 of the remaining 12 cases yielded insufficient material on one or more attempts. Nine patients, for various reasons, were not biopsied.

Since the effective dosage of equine gonadotropie hormone in the human being is not definitely known (Hart and Cole<sup>52</sup> found that ovarian weight rather than the body weight is the criterion for determining comparative doses in animals), treatment was given with greatly varying doses in several different ways:

1. A single injection of this hormone was given on the seventh to the twelfth day of the menstrual cycle. An injection contained 200 to 600 rat units.
2. A course, consisting of 4 to 10 injections, was given daily or on alternate days, usually in the early part of the cycle, just previous to the time when ovulation was expected to occur.
3. Courses were given in the same way, but chorionic gonadotropie hormone (C.G.H.) was given in 500 rat unit doses with each injection of equine gonadotropie hormone.
4. Courses of equine gonadotropie hormone followed immediately by courses of equine gonadotropie hormone and chorionic gonadotropie hormone were tried.
5. Combinations of courses of equine gonadotropie hormone preceded by, concurrently with, or followed by synthetic estrogen or estrogenic hormone were given.

The intravenous route of administration was employed in 18 patients and the intramuscular method in the others. Chorionic gonadotropie hormone was given intramuscularly. Before each course of injections, patients were skin-tested for sensitivity to horse serum. We feel that this is wise despite the fact that equine gonadotropie hormone preparations have been highly purified and the protein content greatly reduced, and despite Hawkinson's<sup>49</sup> statement that skin testing "seems to be obviated after demonstrating that rabbits, previously sensitized with injections of gonadin, showed no evidence of serum protein reaction after injection of one cubic centimeter of gonadin intravenously." Three of our patients (U 142, U 681 and U 1346) showed such strongly positive skin tests, after receiving from one to five courses of equine gonadotropie hormone, that further similar therapy was omitted. Another patient (U 1790) had urticaria at the site of injection following therapy. Four other patients complained of nausea and vomiting, abdominal pain, headache or backache which they attributed to the injections.

Careful study of the fact that three patients showed the presence of cysts of the ovary after treatment with equine gonadotropie hormone, has failed to convince us that there was any causal connection between the treatment and the diseased condition. However, Sevringshaus<sup>21, 51, 46</sup> warns that continuous therapy with equine gonadotropie hormone can cause cystic follicles in the monkey ovaries, and may do so in the human ovaries. Watson<sup>41</sup> feels convinced that equine gonadotropie hormone therapy resulted in cysts of the ovaries in his cases. Therefore, this possibility must be kept in mind.

TABLE I. STERILITY TREATED WITH EQUINE GONADOTROPIC HORMONE ALONE

| PA-TIENT | AGE | YEARS MAR-RIED | CHIEF COM-PLAINT | PHYSICAL ABNORMALITIES AND OPERATIONS                                  | MENSTRUAL HABIT                | STERILITY WORKUP  | THY-ROID    | EQUINE GONADOTROPIC HORMONE   | RESULTS   |
|----------|-----|----------------|------------------|--|--------------------------------|---|-------------|---|---|
| U1852    | 28  | 2              | Sterility 2 yr.  | Negative B.M.R. -6   | Normal period every 28-32 days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulmer: Motile sperm found<br>Husband: Normal | —           | *1200 R.U. 5 doses<br>8th-12th days<br>1200 R.U. 5 doses<br>8th-12th days   | No change<br>No change                                    |
| U1794    | 25  | 5              | Sterility 5 yr.  | Obese B.M.R. -1  | Normal period every 28 days    | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulmer: Motile sperm found<br>Husband: Normal | 1 gr. daily | 800 R.U. 2 doses<br>8th-9th days<br>2400 R.U. 5 doses<br>8th-12th days  | No change<br>No change                                    |
| U1781    | 27  | 6              | Sterility 6 yr.  | Obese 1922 Appendectomy with drainage B.M.R. +23                       | Normal period every 28 days    | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulmer: Motile sperm found<br>Husband: Normal | —           | 1200 R.U. 5 doses<br>8th-12th days<br>1200 R.U. 5 doses<br>8th-12th days  | No change<br>No change                                    |
| 2182     | 30  | 1½             | Sterility 1½ yr. | Negative 1923 Appendectomy 1939 D. & C., resection ovaries, suspension | Normal period every 28 days    | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulmer: Motile sperm found<br>Husband: —      | —           | 1200 R.U. 5 doses<br>8th-12th days  | No change   |
| 1005     | 23  | 5              | Sterility 1½ yr. | Negative 1936 D. & C.<br>1938 Vag. Hys. for missed abortion<br>4 mo.   | Normal period every 26-28 days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulmer: Motile sperm found<br>Husband: Normal | 1 gr. daily | 200 R.U. 12th day<br>1200 R.U. 5 doses<br>8th-12th days<br>1200 R.U. 3 doses<br>7th-9th-11th days<br>2000 R.U. 4 doses<br>7th-10th days | No change<br>No change<br>Period 8 days late<br>No change |

\*Intravenous.

TABLE I—CONT'D

| PA-TIENT | AGE | YEARS MAR-RIED | CHIEF COM-PLAINT  | PHYSICAL ABNORMALITIES AND OPERATIONS                         | MENSTRUAL HABIT                                     | STERILITY WORKUP  | THYROID                            | EQUINE GONADOTROPIC HORMONE   | RESULTS                                       |
|----------|-----|----------------|---|---|---|---|------------------------------------|---|---|
| U681     | 30  | 10             | Sterility 6 yr.<br>1930<br>Misc. 7 mo.<br>1933<br>Abo. 3 mo.  | Negative<br>1931 Appendectomy<br>1933 Suspension<br>B.M.R. -7 | Irregular periods every 26-39 days, often prolonged | Biopsy: Proliferative endometrium<br>Rubin: -<br>Hulmer: 1 test unsatisfactory<br>Husband: Normal | 1 gr. daily                        | 1200 R.U. 5 doses<br>14th-18th days   | No change<br>Biopsy: endometrium<br>No change |
| U1870    | 28  | 9              | Sterility 6 yr.<br>Normal delivery, full term, 1933           | Negative  | Normal period every 25-26 days                      | Biopsy: Secretory endometrium<br>Rubin: -<br>Hulmer: Tubes patent<br>Husband: Motile sperm found  | 1200 R.U. 5 doses<br>8th-12th days | No change   |   |
| 2139     | 36  | 1              | Sterility 1 yr.<br>1939<br>abortion 6 wk. ?                   | Negative  | Normal period every 25-28 days                      | Biopsy: -<br>Rubin: -<br>Hulmer: Motile sperm found<br>Husband: -                                 | 1½ gr. daily                       | *200 R.U. 9th day   |   |
| 2013     | 27  | 3              | Sterility 1 yr.<br>Dia-phragm 2 yr.                           | Negative<br>1939 D. & C.<br>B.M.R. -3 to +2                   | Normal period every 29-34 days                      | Biopsy: Secretory endometrium<br>Rubin: -<br>Hulmer: Motile sperm found<br>Husband: -             | 1 gr. daily                        | *100 R.U. 7th day<br>400 R.U. 7th day<br>1800 R.U. 4 doses<br>8th-10th-12th-13th days |   |
| 890      | 26  | 5              | Sterility 2½ yr.<br>Condom 1 yr.<br>Rhythm and douches 1½ yr. | Negative<br>1938 Conization<br>B.M.R. +4                      | Normal period every 26-28 days                      | Biopsy: None<br>Rubin: -<br>Hulmer: Motile sperm found<br>Husband: Oligospermia                   | -                                  | *200 R.U. 10th day  |   |

|      |    |    |                              |  |   |                                     |   |  |
|------|----|----|------------------------------|--|---|-------------------------------------|---|--|
| 705  | 34 | 7  | Sterility 7 yr.              | Negative 1938 D. & C, resection both ovaries, suspension, appendectomy | Periods irregular for 5 years; every 30-40 days last year | Biopsy: Rubin: Huhner: Husband: -   | Proliferative endometrium 1½ gr. daily *100 R.U. 15th day *300 R.U. 9th day | No change Biopsy: 4 mo. later, secretory endometrium             |
| 2369 | 39 | 11 | Sterility 3 yr. 1928         | Negative   | Normal period every 28-32 days                            | Biopsy: - Rubin: Huhner: Husband: - | 1 gr. daily 1800 R.U. 4 doses 9th-12th days                                 | No change  |
| 1022 | 30 | 6  | Sterility 6 yr.              | Negative 1930 Appendectomy 1937 Hymenectomy                            | Normal period every 26-29 days                            | Biopsy: Rubin: Huhner: Husband: -   | *100 R.U. 10th day  | No change  |
| 2156 | 24 | 7  | Sterility 3 yr. Condom 4 yr. | Negative   | Normal period every 28-29 days                            | Biopsy: Rubin: Huhner: Husband: -   | 400 R.U. 11th day   | Flowed 8 days later Biopsy: 27 days later; Secretory endometrium |

TABLE IA. STERILITY TREATED WITH EQUINE GONADOTROPIC HORMONE AND ESTROGEN

| PA-TIENT | AGE | YEARS MAR-RIED | CHIEF COM-PLAINT                             | PHYSICAL ABNORMALITIES AND OPERATIONS | MENSTRUAL HABIT                | STERILITY WORKUP   | THY-ROID    | E.G.H. AND ESTROGENIC SUBSTANCE   | RESULTS                                    |
|----------|-----|----------------|--|---------------------------------------|--------------------------------|--|-------------|---|--|
| 2248     | 33  | 9              | Sterility 9 yr.                              | Negative                              | Normal period every 25-28 days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Unsatisfactory<br>Husband: Count normal, treated for chronic prostatitis | 1 gr. daily | Stilbestrol 1 mg. daily for 2 cycles. With 1st cycle E.G.H. 1200 R.U. 5 doses 10th-11th days                                | No change                                  |
| 2370     | 33  | 2              | Sterility 2 yr.                              | Negative                              | Normal period every 28 days    | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: Normal                                    | 1 gr. daily | Stilbestrol 1 mg. daily for 2 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days<br>E.G.H. 1200 R.U. 5 doses 7th-11th days | No change                                  |
| 2174     | 37  | 6              | Sterility 6 yr.                              | Negative                              | Normal period every 27-30 days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: Normal                                    | 2 gr.       | Stilbestrol 1 mg. daily $\times$ 30. Then E.G.H. 1200 R.U. 5 doses 8th-12th days  | Period on schedule but profuse and painful |
| 996      | 33  | 4              | Sterility 1½ yr. 1938 D. & C. abortion 3 mo. | Negative                              | Normal period every 26 days    | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: Normal                                    | 1 gr. daily | Stilbestrol 1 mg. daily for 3 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days<br>E.G.H. 1000 R.U. 5 doses 7th-11th days | No change                                  |

\*Intravenous.  
E. G. H., Equine gonadotrophic hormone.  
E., Estrogenic hormone.

|       |    |    |  |                        |                                      |   |   |   |   |
|-------|----|----|--|------------------------|--------------------------------------|---|---|---|---|
| U1771 | 34 | 12 | Sterility<br>11 yr.<br>1927<br>abortion<br>3 mo. | Negative               | Normal period<br>every 28-30<br>days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Huhner: Motile sperm found<br>Husband: Normal | 1 gr.<br>daily  | Stilbestrol 1 mg. daily<br>x 30 and E.G.H.<br>1200 R.U. 5 doses<br>7th-11th days<br>E.G.H. 400 R.U. 1<br>dose 7th day         | No change   |
| U2871 | 26 | 3  | Sterility<br>3 yr.                               | Negative<br>B.M.R. -19 | Normal period<br>every 28-30<br>days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Huhner: Motile sperm found<br>Husband: Normal | 1 gr.<br>daily  | E.G.H. 1600 R.U. 3<br>doses 11th-12th-<br>14th days   | Period on<br>schedule<br>but pro-<br>fuse and<br>prolonged<br>No change |
| U655  | 23 | 5  |  |                        |                                      | Irregular for 5<br>years 28-60<br>days.<br>Period every<br>28-30 days<br>while attend-<br>ing clinic  | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Huhner: Motile sperm found<br>Husband: Normal | Stilbestrol .1 mg.<br>daily for 2 cycles.<br>With 2nd cycle<br>E.G.H. 2400 R.U.<br>4 doses 7th-10th<br>days                   | No change   |
| 2334  | 34 | 2½ | Sterility<br>1 yr.<br>1938<br>abortion<br>3 mo.  | Negative               | Normal period<br>every 25-28<br>days | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Huhner: Motile sperm found<br>Husband: Normal | 3 gr.<br>daily  | Stilbestrol .1 mg.<br>daily x 55. With<br>2nd cycle E.G.H.<br>1200 R.U. 5 doses<br>8th-12th days                              | No change   |
|       |    |    |  |                        |                                      |   | ½ gr.<br>daily  | Stilbestrol 1 mg. daily<br>x 20 and E.G.H.<br>1200 R.U. 5 doses<br>8th-12th days<br>E.G.H. 1200 R.U. 5<br>doses 8th-12th days | No change   |

TABLE IA—Cont'd

| PA-TIENT | YEARS MAR-RIED | CHIEF COM-PLAINT | PHYSICAL ABNORMALITIES AND OPERATIONS  | MENSTRUAL HABIT  | STERILITY WORKUP  | THYROID   | E.G.H. AND ESTROGENIC SUBSTANCE  | RESULTS   |
|----------|----------------|------------------|--|--|---|---|--|-----------|
| 2265     | 25             | 5                | Sterility 3 yr. 1936<br>Negative 1931 appendectomy<br>1938 D. & C.<br>misse, 6 1/2 mo. | Normal period every 28 days<br>Biopsy: Proliferative endometrium<br>Rubin: Tubes patent<br>Hulner: Unsatisfactory<br>Husband: Normal | 1 gr. daily   | E. 600 I.U. daily for 2 cycles. With 2nd cycle E.G.H. 1200 R.U. 5 doses 7th-11th days | No change  |           |
| 2099     | 37             | 9                | Sterility 9 yr.  | Normal period every 33-35 days   | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: —      | —   | E. 600 I.U. daily for 3 cycles. Then *E.G.H. 800 R.U. 3 doses 9th-11th-13th days | No change |
| 2264     | 34             | 2                | Sterility 3 yr. 1936, normal delivery full term  | Normal period every 28-30 days   | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: —      | 1 gr. daily   | E. 2000 I.U. daily for 3 cycles. Then E.G.H. 1200 R.U. 5 doses 7th-11th days     | No change |
| 2115     | 38             | 13               | Sterility 13 yr. 1 1/2 yr. since resection l. ovary, suspension                        | Irregular period every 25-52 days  | Biopsy: Secretory endometrium<br>Rubin: Tubes patent<br>Hulner: Motile sperm found<br>Husband: Normal | 1 gr. daily   | E. 600 I.U. daily $\times$ 28. Then E.G.H. 1200 R.U. 5 doses 8th-12th days       | No change |

Each of our patients was examined in the gynecologic clinic before presenting herself at the endocrine clinic, and all abnormalities such as retroversion, infected cervixes, vaginitis, etc., were taken care of. Thyroid was given to most of the patients, even without determination of the basal metabolic rate, unless there were definite contraindications.

#### GROUP I. STERILITY (TABLES I AND IA)

In this group of 26 patients, the ages varied from 23 to 39, and the duration of sterility from one to eleven years. Ten patients were known to have been pregnant one or more times before, and 3 of these had had full-term deliveries. Eight had had abdominal operations. All but 3 had "normal" regular periods. There were 3 cases with anovulatory cycles, and 20 with ovulatory cycles as shown by biopsy. Of the remaining 3 cases, 1 patient became pregnant before biopsy could be done, and the other 2 were not biopsied. Patency of the tubes was proved by insufflation in all cases except one in which no Rubin test was made. Motile sperm were found in the cervix four to twenty hours following coitus in all but 3 patients, and the husbands in these cases were examined and found to be normal. Husbands were given complete physical examinations in most instances, and semen specimens alone were examined in others.

The group is divided into two parts on the basis of therapy. The purpose of giving the equine gonadotrophic hormone was to repeat the work of Hall<sup>48</sup> and of Davis and Koff,<sup>42</sup> i.e., to stimulate the ovaries and cause multiple ovulation if possible, in the hope of increasing the chances of pregnancy. The addition of estrogenic hormone or synthetic estrogen in the cases in Table IA was intended to prime the genital system or act as a tonic to it, and thus to aid impregnation. It was also given in order to duplicate conditions of clinical experiments done elsewhere.

Results were very disappointing. One patient (Case 2139) became pregnant immediately following a course of equine gonadotrophic hormone. However, as this patient only two months before had had an unusually heavy flow two weeks after her period was due, which had been diagnosed as a possible abortion, we do not feel that her pregnancy was related to the therapy. One of the patients with anovulatory bleeding (705) had a secretory endometrium four months after treatment, but as the total amount of equine gonadotrophic hormone received was only 400 R.U., given in two monthly injections, it seems more reasonable to us to assume that she had occasional anovulatory cycles which, as Rock, Bartlett and Matson<sup>54</sup> and Novak<sup>22</sup> point out, are not unusual.

In 2 patients (Cases 1022 and 2013), cysts of the ovaries were noted following treatment. Both followed the intravenous injection of only 100 R.U. of equine gonadotrophic hormone. In Case 1022, painful and enlarged ovaries were not found until seven months after treatment. At laparotomy, three months later, ten months after treatment, follicular cysts were excised from both ovaries, and the patient became pregnant one month later, which is not uncommon under these conditions.<sup>28</sup> In Case 2013, a cyst was not noted until four months after treatment. It was purposely ruptured while the patient was having a dilatation and curettage. Six months later, and two months after 400 R.U. more of equine gonadotrophic hormone had been given, the ovary again was noted to be cystic.

There was no noteworthy change in the remaining twenty-two patients after equine gonadotrophic hormone administration.

#### GROUP II. DYSFUNCTIONAL FLOWING (TABLE II)

This group consists of 6 patients ranging in age from 14 to 28. Three were single and 3 married, with no known pregnancies. Four had had one or more curettages. Dysfunctional flowing had persisted from eighteen months to eight years. Biopsies were omitted on 2 patients aged 14 and 16 with unruptured hymens. Of the remaining 4 patients, 2, prior to treatment, showed proliferative endometrium with dysplasia, one had hyperplasia, and the last had a normal

TABLE II. DYSFUNCTIONAL BLEEDING TREATED WITH EQUINE AND CHORIONIC GONADOTROPIC HORMONES

| PA*<br>PATIENT | AGE | MARI-<br>TAL<br>STA-<br>TUS | CHIEF<br>COM-<br>PLAINT                 | PHYSICAL<br>ABNORMALITIES<br>AND<br>OPERATIONS                                     | MENSTRUAL HABIT   | PREVIOUS<br>THERAPY   | THY-<br>ROID  | HORMONE THERAPY   | RESULTS  |
|----------------|-----|-----------------------------|---|--|---|---|---|---|--|
| U2875          | 14  | S                           | Dys-<br>func-<br>tional<br>flow-<br>ing | Negative<br>B.M.R. -17   | Frequent prolonged<br>periods of flow for<br>2 years. Persistent<br>flowing for 3<br>months | No biopsy<br>one propionate in-<br>effective  | 2 gr.<br>daily  | *E.G.H. 600 R.U. and<br>C.G.H. 1500 R.U. in<br>3 doses while flowing  | Flow stopped day after<br>last injection for 8<br>days. Then 10 days<br>flowing, 6 days no<br>flow, 5 days flow<br>Amenorrhea 3 months<br>No biopsy<br>No evidence of ovula-<br>tion |
| U2876          | 23  | S                           | Dys-<br>func-<br>tional<br>flow-<br>ing | Negative<br>1933 D. & C.,<br>Rt. oophorec-<br>tomy, appen-<br>dectomy<br>B.M.R. -4 | Prolonged periods for<br>6 years. Past year<br>only 3-10 days be-<br>tween periods          | Biopsy: Proliferative<br>endometrium with<br>dysplasia. C.G.H.,<br>"Maturity Fac-<br>tor," theelin<br>ineffective | *E.G.H. 800 R.U. in 4<br>doses alt. days while<br>flowing; 1 week later<br>*E.G.H. 800 R.U. &<br>C.G.H. 2000 R.U. in<br>4 doses alt. days | *E.G.H. 600 R.U. &<br>C.G.H. 1500 R.U. in<br>3 doses alt. days<br>Flow stopped for 5<br>days<br>No evidence of ovula-<br>tion |  |

\*Intravenous.

E. G. H., Equine gonadotrophic hormone,  
C. G. H., Chorionic gonadotrophic hormone.

|       |    |               |                       |                                  |   |  |  |   |
|-------|----|---------------|-----------------------|----------------------------------|---|--|--|---|
| U1797 | 27 | Married 6 yr. | Dysfunctional flowing | Negative 1936 D. & C. B.M.R. -11 | For 8 years irregular periods lasting from 10 days to a month   | Biopsy: Proliferative endometrium with daily dysplasia. X-ray, C.G.H., testosterone propionate ineffective | *E.G.H. 1000 R.U. in 4 doses alt. days 23rd-30th days  | Flowed after first injection and continued for 18 days  |
| U1863 | 28 | Married 5 yr. | Dysfunctional flowing | Obese 1938 D. & C. B.M.R. -8     | For 22 months prolonged periods and intermenstrual staining. Relieved by D. & C. for 1 month                    | Biopsy: Proliferative endometrium with hyperplasia   | E.G.H. 1200 R.U. in 5 doses daily 23rd-27th days   | Profuse and prolonged flow 3 days, beginning 3 days later Biopsy: Proliferative endometrium. No evidence of ovulation |
| 2143  | 20 | Married 1 yr. | Dysfunctional flowing | Negative 1934 D. & C. Appendix   | Always very irregular. For 3 years prolonged periods  | Biopsy: Proliferative endometrium  | E.G.H. 1000 R.U. in 5 doses 6th-10th days followed by Stillestrol 1 mg. daily $\times$ 9   | No change in menstrual habit. No evidence of ovulation  |
| U142  | 16 | S             | Dysfunctional flowing | Uterus small B.M.R. +7 Hg 54%    | Periods every 28 days for 2 years. For last 1 1/2 years. Periods lasting 2 to 3 weeks with 2 to 3 week interval | No biopsy  | *E.G.H. 600 R.U. & C.G.H. 1500 R.U. in 3 doses alt. days while flowing, then Testosterone Propionate 6 c.c. in 3 doses alt. days | Still flowing 2 weeks later and more profusely  |
|       |    |               |                       |                                  |   |  | Then *E.G.H. 2400 R.U. & C.G.H. 3000 R.U. in 6 doses alt. days   | Flow ceased for 2 weeks after 3 injections No evidence of ovulation   |

TABLE III. AMENORRHEA TREATED WITH EQUINE AND CHORIONIC GONADOTROPIC HORMONES

| PA-TIENT | AGE | MARI-TAL STA-TUS | CHIEF COM-PLAINT      | PHYSICAL ABNORMALITIES* AND OPERATIONS                                 | MENSTRUAL HABIT   | BIOPSY      | HORMONE THERAPY  | THY-ROID   | RESULTS     |  | BIOPSY  |
|----------|-----|------------------|-----------------------|--|---|-------------|--|--|-------------|--|---|
|          |     |                  |                       |  |   |             |  |  | 3 gr. daily | *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days |   |
| U1853    | 18  | S                | Amenorrhea (pri-mary) | Hypoplasia of genital organs B.M.R. -30 to -17                         | Never menstruated Biopsy: no material obtainable at D. & C.                 |             | Stilbestrol 1 mg. daily $\times$ 7   | Flowed 1 time during administration and after withdrawal | No flow     | No evidence of ovulation                                   | Insufficient tissue                           |
| U1792    | 25  | S                | Amenorrhea (pri-mary) | Hypoplasia of genital organs B.M.R. +17 to +1                          | Never menstruated Biopsy: no material obtainable in 2 attempts              | 2 gr. daily | *E.G.H. 800 R.U. in 4 doses alt. days  | No flow  | No flow     | No evidence of ovulation                                   | Prolif. End.                                  |
| U1790    | 22  | S                | Amenorrhea (pri-mary) | Hypoplasia of genital organs B.M.R. -16                                | Never menstruated No biopsy   | --          | *E.G.H. 1200 R.U. in 5 daily doses   | No flow  | No flow     | No evidence of ovulation                                   | No evidence of ovulation                      |
| U1791    | 22  | S                | Amenorrhea (pri-mary) | Hypoplasia of genital organs Masculine distribution of hair B.M.R. -16 | Few scanty periods since onset at 15 days Biopsy: Proliferative endometrium | 3 gr. daily | Stilbestrol 1 mg. daily $\times$ 21 Then E.G.H. 1200 R.U. in 5 doses 7th-11th days | Withdrawal bleeding No flow                              | No flow     | No evidence of ovulation                                   | No evidence of ovulation                      |
| U1783    | 23  | S                | Amenorrhea            | Hypoplasia of genital organs B.M.R. -28                                | No periods for 2 years Biopsy: Hypoplasia                                   | 3 gr. daily | *E.G.H. 1000 R.U. in 4 doses alt. days   | No flow  | No flow     | No evidence of ovulation                                   | 2 wk. later hypoplasia 3 wk. later hypoplasia |

\*Intravenous.

E.G.H., Equine gonadotropin hormone.

C.G.H., Chorionic gonadotropin hormone.

Flowed 5 days during 1 week of injection.

U2846 22 18 | Amen- | Negative | One period at age of  $\frac{3}{4}$  gr. | \*E.G.H. 1600 R.U. in 8 doses | Prolif. End.U2846 22 18 | Amen- | Negative | One period at age of  $\frac{3}{4}$  gr. | \*E.G.H. 1600 R.U. in 8 doses | Prolif. End.

|       |    |               |                      |   |   |  |
|-------|----|---------------|----------------------|---|---|--|
| U2846 | 22 | 8             | Amenorrhea B.M.R. -8 | Negative B.M.R. -8  | One period at age of $\frac{3}{4}$ gr. *E.G.H. 1600 R.U. in 8 doses twice weekly          | Flowed 5 days during last week of injections |
|       |    |               |                      |   | Biopsy: Proliferative endometrium with dysplasia  |  |
| U1805 | 28 |               |                      |   | Always irregular. For 1 gr. daily   | No flow                                      |
|       |    |               |                      |   | Then *E.G.H. 1600 R.U. in 8 doses   | No flow                                      |
|       |    |               |                      |   | 1 time weekly   | Prolif. End.                                 |
|       |    |               |                      |   | *E.G.H. 1200 R.U. in 6 daily doses  |  |
|       |    |               |                      |   | E.G.H. 2000 R.U. in 10 daily doses  |  |
|       |    |               |                      |   | followed by E.G.H. 2500 R.U.  |  |
|       |    |               |                      |   | and C.G.H. 5000 R.U. in 10 daily doses  | No flow                                      |
| U1747 | 23 | Married 2 yr. | Amenorrhea           | Obese Hypoplasia of genital organs 1927 Appendectomy B.M.R. +15               | E.G.H. 1200 R.U. in 5 daily doses   | No evidence of ovulation                     |
|       |    |               |                      |   | E.G.H. 2200 R.U. in 5 daily doses   |  |
|       |    |               |                      |   | 25 days later 3 day Hypoplastic Prolif. End.  |  |
|       |    |               |                      |   | No evidence of ovulation  |  |
| U1692 | 25 | Married 2 yr. | Amenorrhea           | Obese   | *E.G.H. 1000 R.U. in 4 doses alt. days  | No flow                                      |
|       |    |               |                      |   | E.G.H. 1000 R.U. in 4 doses alt. days   |  |
|       |    |               |                      |   | No evidence of ovulation  |  |
|       |    |               |                      |   | 1, 3, and 5 weeks later —Prolif. End.   |  |
| U1691 | 32 | Married 9 yr. | Amenorrhea           | Hypoplasia of genital organs Moderately hirsute 1934 Appendectomy 3 B.M.R. +8 | For past 2 years periods scanty and about every 3 months No biopsy                        | No evidence of ovulation                     |
|       |    |               |                      |   | E.G.H. 1200 R.U. in 5 doses 6th-10th days   |  |
|       |    |               |                      |   | Stilbestrol 1 mg. daily $\times$ 14 followed by E.G.H. 1200 R.U. in 5 doses 8th-12th days |  |
|       |    |               |                      |   | Stained 12 days later   |  |
|       |    |               |                      |   | Flowed 5 days, 1 week after beginning Stilbestrol   |  |
|       |    |               |                      |   | 28 days later stained Then amenorrhea 5 months  |  |
|       |    |               |                      |   | No evidence of ovulation  |  |
|       |    |               |                      |   | Insufficient tissue   |  |

TABLE III—CONT'D

| PA-TIENT | AGE | MARITAL STATUS | CHIEF COM-PLAINT            | PHYSICAL ABNORMALITIES AND OPERATIONS                           | MENSTRUAL HABIT   | BIOPSY                                     | HORMONE THERAPY  |                                     | RESULTS   | BIOPSY                 |
|----------|-----|----------------|-----------------------------|---|---|--|--|-------------------------------------|---|------------------------|
|          |     |                |                             |   |   |  | 3 gr. daily  | E. G. H. 1200 R.U. in 5 daily doses |   |                        |
| U1866    | 30  | Married 3 yr.  | Amenorrhea                  | Obese Hypoplasia of genital organs Biopsy: Hypoplasia B.M.R. -8 | Last period 3 years ago   |  | Stilbestrol 0.1 mg. daily $\times 14$  | No flow                             |   | Refused                |
| U2848    | 28  | Married 7 yr.  | Amenorrhea 1932             | Obese B.M.R. +1   | For 4 yr. occasional period. Last period 3 months ago (1st in 14 mo.)     |  | E.G.H. 2000 R.U. and C.G.H. 2500 R.U. in 5 doses alt. days   | No flow                             |   |                        |
|          |     |                | abortion 3 mo.              |   | Biopsy: Atrophy or Hypoplasia   |  | *E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days   | No flow                             |   |                        |
|          |     |                | 1934, normal delivery, term |   |   |  | *E.G.H. 3600 R.U. in 6 doses alt. No flow  |                                     |   |                        |
| 1036     | 25  | Married 2½ yr. | Amenorrhea                  | Hypoplasia of genital organs 1938 D. & C. B.M.R. +5             | Regular periods till 6 yr. ago. D. & C. in 1938 with 1 period 2 mo. later | 1 gr. daily                                | Stilbestrol 1 mg. daily for 5 months   | No flow                             |   |                        |
|          |     |                |                             | No biopsy   | No period in 2½ yr.   | Then E.G.H. 1200 R.U. in 3 doses alt. days | No evidence of ovulation   |                                     |   |                        |
| 2175     | 24  | Married 2 yr.  | Amenorrhea                  | Negative B.M.R. -20 to -7                                       | Biopsy: None  | 1½ gr. daily                               | E.G.H. 1000 R.U. in 4 doses alt. days  |                                     | Periods began 3 months later (29 months after beginning thyroid) every 33-36 days | later—<br>Prolif. End. |
|          |     |                |                             |   |   |  | E.G.H. 1200 R.U. in 3 doses 8th. 10th days followed by E.G.H. 1200 R.U. and C.G.H. 3000 R.U. in 3 doses 11th-13th days | Period every 24 days                |   |                        |
|          |     |                |                             |   |   |  |  | # ovulation                         |   |                        |

|       |    |               |   |   |   |  |                          |
|-------|----|---------------|---|---|---|--|--------------------------|
| U1021 | 34 | Married 9 yr. | Amenorrhea 1939 D. & C. normal B.M.R. -21 to -6 | No period since child born 8 yr. ago. Ooc. daily with intensive therapy with C.G.H., estrone, pituitary extracts, etc. Biopsy: Hypoplasia | *E.G.H. 1000 R.U. in 4 doses alt. for 2 days<br>*E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days for 5 days<br>E.G.H. 1600 R.U. in 4 doses alt. Flowed 8 days later for 4 days<br>E.G.H. 1600 R.U. in 4 doses alt. No flow  | Flowed 3 weeks later for 2 days<br>1 week later Hypoplasia | Prolif. End.             |
| U1346 | 25 | Married 3 yr. |   | Hypoplasia of genital organs B.M.R. -2  | *E.G.H. 800 R.U. in 4 doses alt. No flow<br>*E.G.H. 800 R.U. in 4 doses alt. No flow<br>*E.G.H. 800 R.U. and C.G.H. 2000 R.U. in 4 doses alt. days<br>*E.G.H. 2400 R.U. in 6 doses alt. Stained 4 days after Hypoplasia last injection<br>*E.G.H. 2400 R.U. and C.G.H. 3000 R.U. 6 doses alt. days<br>Stilbestrol 1 mg. daily $\times$ 21 days<br>Then E.G.H. 1200 R.U. in 4 doses 6th-9th days followed by<br>E.G.H. 1200 R.U. and C.G.H. No flow<br>4000 R.U. in 4 doses 10th-13th days<br>E.G.H. 2750 I.U. in 11 daily doses 8 days later flowed for 5 days<br>followed by | Hypoplasia<br>Hypoplasia                                   | Prolif. End.             |
|       |    |               |   |   | E.G.H. 2800 R.U. and C.G.H. 7000 R.U. in 7 daily doses.   | Atypical Prolif. End.                                      | No evidence of ovulation |

proliferative endometrium. Three of the patients received equine gonadotropic hormone alone, and three also received chorionic gonadotropic hormone to act as a luteinizing agent or to aid ovulation synergistically, as recommended by Fluhmann<sup>24</sup> and Evans.<sup>9</sup>

The results in this group were uniformly unsatisfactory. One patient, Case U 2875, 14 years of age, after thirty days of alternate flow and cessation of flow following a course of equine gonadotropic hormone and chorionic gonadotropic hormone, developed an amenorrhea which has persisted for three months. Another patient, Case U 142, 16 years of age, had continuous flowing after a course of equine gonadotropic hormone and chorionic gonadotropic hormone. This was followed in two weeks by three injections of testosterone propionate. As there was still no cessation of flow, another course of equine gonadotropic hormone and chorionic gonadotropic hormone was given and the bleeding stopped for two weeks. On resumption of the flow, the skin test was positive for gonadotropin. In the following six months, two curettages were necessary and showed hyperplasia of the endometrium. Ultimately radium was required to stop the excessive loss of blood. Two patients, Cases U 1863 and U 1797, had a more profuse flow following treatment. One, Case U 1863, required progesterone to arrest the bleeding, and biopsy showed a proliferative endometrium. The other, Case U 1797, received x-ray treatment three months later, and regular periods, average in amount, have continued for a year. Two patients showed no change following therapy.

#### GROUP III. AMENORRHEA (TABLE III)

This group is composed of 16 patients from 18 to 32 years of age. There were 3 cases of primary amenorrhea, and the duration of amenorrhea in the other patients varied from three months to eight years. Ten of the patients were married and 3 had been pregnant. The basal metabolic rates varied from minus 30 to plus 17. Satisfactory endometrial biopsies were obtained in 9 cases prior to treatment. Seven showed hypoplasia and 2 proliferative endometrium, one with dysplasia. Biopsies were attempted in 3 other cases on one or more occasions, but sufficient tissue could not be obtained. This would indicate hypoplasia. In 4 cases no biopsy was taken. Eleven patients had hypoplasia of the genital organs.

Four patients received equine gonadotropic hormone alone, and the others received either estrogenic or chorionic gonadotropic hormones in addition. The minimum total dosage of equine gonadotropic hormone given in a course of injections was 1,000 R.U. and the maximum, 2,800 R.U. and 2,750 I.U. of equine gonadotropic hormone preparations, in 18 consecutive daily injections. We gave this large dose only very recently to one patient, Case U 1346, because with the recommended dosage our results had been so unsatisfactory. (Frank<sup>40</sup> and Büttner<sup>44</sup> consider it justifiable and even necessary to try very high dosages of gonadotropic preparations.) Eight days after the last injection, the patient flowed for five days. Biopsy obtained on the day before flow showed atypical proliferative endometrium, indicating that the patient had not ovulated.

An endometrial biopsy was obtained following each of 16 separate series of equine gonadotropic hormone injections in 9 patients, and in all instances it showed proliferative endometrium, usually with hypoplasia.

Of the 3 cases of primary amenorrhea, one patient flowed for a few days during, and again at the termination of seven months of daily administration of stilbestrol, but with equine gonadotropic hormone alone, there was no flow in any of the 3 cases. Of the 13 cases of secondary amenorrhea, 7 patients were unchanged and 6 had one or more periods of staining or flow, viz., Case U 2846, 22 years of age, had had one period at the age of 18. Prior to therapy she had a proliferative endometrium with dysplasia. While receiving equine gonadotropic hormone in dosages of 200 R.U. by injection, twice weekly, she had a five-day flow. Three later courses of equine gonadotropic hormone, one with large dosage, produced no flow, and a subsequent biopsy showed a proliferative endometrium. Case U 1805, a 28-year-old married woman, had had no periods and only occasional staining for five years. Biopsy before treatment showed hypoplasia. Twenty-five days after a second course of equine gonadotropic hormone she flowed for three days from a hypoplastic endometrium. (This patient was given a three months' vacation and only re-

cently returned to the clinic to say that she had had a period during each of the three months. It is possible that these periods were ovulatory in character, but spontaneous return of the menses is not rare in secondary amenorrhea. Franks<sup>40</sup> cites 7 cases of amenorrhea, one of 17 years' duration, in which menstruation returned during a study period prior to treatment.) In one patient (U 1692), there was staining on two occasions after courses of equine gonadotropic hormone, but when last seen, the patient reported no traces of menstruation for five months. The patient in Case U 1346 stained for four days after a course of equine gonadotropic hormone and chorionic gonadotropic hormone, and flowed for five days after a very large dose of equine gonadotropic hormone followed by equine gonadotropic hormone combined with chorionic gonadotropic hormone. In both instances flow was from a proliferative endometrium which in one instance showed hypoplasia. The patient in Case U 1021, a 34-year-old woman who had not flowed in the eight years following the birth of a child, had three periods of flow: Two following equine gonadotropic hormone injections alone and one after administration of a course of equine gonadotropic hormone and chorionic gonadotropic hormone. Twice, flow was from a proliferative endometrium, one with hypoplasia. Another biopsy, two months later, also showed hypoplasia. Patient, Case 2175, was 24 years of age and had had no period in two and one-half years. No biopsy was obtained prior to treatment. The basal metabolic rate was minus 20. One course of equine gonadotropic hormone produced no results. Thyroid was given, and two months later the patient began to flow every thirty-three to thirty-six days. Biopsy showed a proliferative endometrium, so a course of equine gonadotropic hormone combined with chorionic gonadotropic hormone was given. The next three periods were about twenty-four days apart. No biopsy was obtained to prove ovulation nor has the patient become pregnant in the past year. The low basal metabolic rate which was corrected by thyroid seems to us to be the probable cause of the irregularity.

In one patient in this group, a cyst of the ovary appeared following equine gonadotropic hormone therapy. The patient in Case U 2848, 28 years of age, had a full-term child in 1934. Since then she has had an occasional period, but only one in the seventeen months prior to treatment. There was no flow following a course of equine gonadotropic hormone combined with chorionic gonadotropic hormone, and another course of equine gonadotropic hormone alone. One week following treatment, examination showed no signs of a cyst, but two months later, with no treatment in the interim, a cyst was palpated and was ruptured at examination. Sixteen days later, the patient began to flow and the period in the next month was proved to be from a secretory endometrium. She has not become pregnant in nine months, but her periods have continued to be regular.

#### SUMMARY

1. A gonadotropic substance obtained from the serum of pregnant mares has stimulated ovulation in immature laboratory animals.
2. It is reported to have produced ovulation and multiple ovulation in both the normal and abnormal human ovary, with gratifying results in cases of sterility, dysfunctional flow, and amenorrhea.
3. This study deals with a series of 48 cases of sterility, dysfunctional flowing, and amenorrhea treated with equine gonadotropic hormone. Sixteen patients were not ovulating, as proved by endometrial biopsy, and 9 others clinically were not ovulating. Twenty patients were ovulating, as shown by biopsy, and 3 were clinically ovulating. Effects of treatment were judged in 12 cases by endometrial biopsy and by subsequent clinical course in the others.
4. Thirty-nine patients (81.2 per cent) were apparently unaffected by equine gonadotropic hormone.
5. In no case was there any definite evidence of stimulation of ovulation by equine gonadotropic hormone. In the sterility group there was one pregnancy, but we feel it cannot be attributed to equine gonado-

tropic hormone. One other, an anovulatory patient, was found by biopsy to be ovulating four months after treatment. One patient with dysfunctional bleeding continued to flow for a month following equine gonadotrophic hormone therapy and since then has had amenorrhea for three months. Six patients with amenorrhea stained or flowed after treatment, but none of these showed evidence of ovulation. Only one patient continued to flow at regular intervals. She seemed to be responding rather to thyroid than to equine gonadotrophic hormone stimulation.

6. Allergic reactions to equine gonadotrophic hormone appeared in 3 patients following therapy, and in 3 patients, a cyst of the ovary was noted following treatment.

#### CONCLUSION

With the varying dosages used in this study, the equine gonadotrophic hormone has not been shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea, nor has it had any apparent effect in cases of sterility. Three cases of cysts of the ovary were noted following therapy. Although we cannot, and do not, attribute them to equine gonadotrophic hormone, we cannot deny the possibility that the treatment may have been instrumental in causing the condition. We believe that a great deal of clinical experimentation is necessary before the value of this hormone will be established.

We are deeply indebted to the Cutter Laboratories, the Schering Corporation, the Winthrop Chemical Company, the Squibb Company, Merck and Company, and Reed and Carnrick for the materials used in this study.

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## LABORATORY AND CLINICAL EXPERIENCE WITH ORAL PREGNENINOLONE\*

MELVIN R. COHEN, M.D., AND IRVING F. STEIN, M.D., CHICAGO, ILL.  
(From the Department of Obstetrics and Gynecology and the Samuel A. Deutsch  
Serum Center, Research Department, Michael Reese Hospital)

UNTIL recently, practically the only orally active hormone was thyroid extract. Although many glandular extracts and residues have been exploited commercially, with few exceptions they have proved to be ineffectual when given by mouth.

Inhoffen and Hohlweg<sup>1</sup> (1938) described two very potent orally active synthetic hormones; 17 Aethinyl Oestradiol, and Pregnen-in-20-on-3-ol 17 (ethinyl testosterone); the first, a potent estrogenic substance, was subsequently discarded because of its accompanying side effects. The second, a progestational substance designated in this report as pregneninolone,<sup>†</sup> was found by them to produce a positive response in infantile rabbits after the administration of but 4 mg. orally. This preliminary report was augmented by the results of other investigators.<sup>2, 5</sup> Clauberg and Ustün<sup>7</sup> observed the action of pregneninolone in the human being; they showed that bleeding associated with glandular cystic hyperplasia could be controlled and the endometrium transformed to a pseudodecidua by the use of prolonon "C."<sup>7</sup> Subsequently, it was found that progestational effects could also be produced by oral pregneninolone in postmenopausal women. Zondek and Rozin<sup>10</sup> found that the effects of oral pregneninolone in the human female were similar to those produced by progesterone hypodermically. Recently, Hamblen and others<sup>13</sup> reported the oral effectiveness of pregneninolone in the treatment of 7 patients with menometrorrhagia. In their study, no alteration in urinary pregnanediol or androgen titer was found.

In order to evaluate this new oral progesterone-like substance, we planned a laboratory and clinical investigation. We first studied the effects of this drug upon the rat in order to coordinate its multiple hormonal action, to observe its effects upon the intact pregnant animal, and to test for toxicity with reference to effects upon the liver and kidney. Clinically, we used the preparation chiefly in those patients who presented a menometrorrhagia. In addition, we used it in some patients complaining of dysmenorrhea, amenorrhea, premenstrual tension, and mazoplasia.

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†Also known as anhydro-oxy-progesterone, Pregneninolone.

‡A brand of pregneninolone.

## EXPERIMENTAL DATA

To test the estrogenic effect of pregnenolone, 5 mature female rats, previously castrated, were fed 10 mg. of the drug on each of two consecutive days. Daily vaginal smears showed complete estrus occurring on the fourth day. Thus pregnenolone shows a qualitative estrogenic action.

To determine the androgenic effects, 3 male rats, aged 2 months, were castrated and fed pregnenolone, 1 mg. daily for ten days, a total of 10 mg. This small dose did not prevent castration changes in the seminal vesicles. However, when 3 male rats, aged two months, were castrated and fed pregnenolone, 2.5 mg. daily for ten days, a total of 25 mg., slight secretory activity occurred in 2 and marked secretory activity was present in the seminal vesicles of the third animal. Two male rats, aged 2 months, fed 5 mg. daily for ten days, showed a more marked androgenic effect. There was marked secretory activity in one, and moderate secretory activity in the seminal vesicles of the second rat. Thus, pregnenolone prevented castration changes in the young male rats when given orally in doses of 25 to 50 mg.

To determine the progestational effect, pseudopregnancy was produced according to the method of Astwood:<sup>4</sup> Mature female rats in full estrus were given faradic stimulation to the cervix. Four days later, the animals were castrated and the endometrium of one uterine horn traumatized with a needle. Ten milligrams of pregnenolone was mixed with their food daily for five days, a total of 50 mg. The animals were then killed and the uteri examined for the presence of decidiomas, with the following results:

| Controls | J                                 | Non-castrate | 4 plus reaction |
|----------|-----------------------------------|--------------|-----------------|
|          | K                                 | Castrate     | No reaction     |
| 19       | Castrate plus 50 mg. pregnenolone |              | 4 plus reaction |
| 22       | Castrate plus 50 mg. pregnenolone |              | 4 plus reaction |
| 2        | Castrate plus 50 mg. pregnenolone |              | 3 plus reaction |
| 19A      | Castrate plus 50 mg. pregnenolone |              | 1 plus reaction |
| 9        | Castrate plus 50 mg. pregnenolone |              | 1 plus reaction |

Thus, 3 out of 5 animals showed strongly positive and the other 2 weakly positive results.

These experiments confirm the work of Emmens and Parkes<sup>8,9</sup> who first described the multiple activities of anhydro-oxy-progesterone (pregnenolone). The androgenic properties which we obtained with this product are comparable to those which Greene, Burrell and Ivy<sup>3</sup> obtained with progesterone.

TABLE I. ORAL PREGNENOLONE IN THE MATURE RAT

| NO. OF ANIMALS | DAILY DOSE MG. | NO. OF DAYS | TOTAL DOSE MG. | OVARIAN WEIGHT MG.   | UTERINE WEIGHT MG.       |
|----------------|----------------|-------------|----------------|----------------------|--------------------------|
| 8              | 0.25           | 20          | 5              | Av. 48               | Av. 320                  |
| 3              | 1.0            | 20          | 20             | 26<br>36<br>50       | Av. 280                  |
| 4              | 5.0            | 20          | 100            | 28<br>32<br>26<br>50 | 216<br>340<br>180<br>380 |
| 6              | 0.5            | 60          | 30             | Av. 48               | Av. 260                  |
| 7              | 1.0            | 60          | 60             | Av. 44               | Av. 240                  |
| 5              | 2.0            | 60          | 120            | Av. 42               | Av. 420                  |
| Controls       |                |             |                | Colony Av. 84        | Av. 340                  |

The effect of oral pregnenolone in the intact adult rat\* is shown in Table I. A series of 33 normal mature female rats were fed pregnenolone in dosages varying from 0.25 mg. to 5 mg. daily for twenty days in one series and for sixty

\*With the assistance of Dr. Charles Freed.

days in the other. The influence upon the uterine and ovarian weights was noted. In all instances, the ovarian weights were markedly reduced even to the point of extreme atrophy in some cases. There was less effect upon the uterus in that the uterine weight was unaffected or decreased in all with the exception of the series which received the largest dose (2 mg. for sixty days: total, 120 mg.). This dose produced a definitely increased uterine weight response well above the normal controls. These results show that pregneninolone inhibits the gonadotropic action of the anterior pituitary gland in intact mature female rats. Pregneninolone in large doses (120 mg.) produced a positive uterine weight response in the presence of ovarian suppression.

To determine the effect of oral pregneninolone on the *intact pregnant rat*, mature rats were mated and daily vaginal smears obtained. The onset of pregnancy was determined by the last estrus, the vaginal plug, and/or microscopic evidence of spermatozoa. Beginning with the fifth day of pregnancy, pregneninolone was fed to animals over a period of six to forty days with a total dosage of from 6 to 200 mg. The effects upon pregnancy and lactation were noted (Table II). It was

TABLE II. PREGNENINOLONE ORALLY IN PREGNANCY (RATS)

| NO. | LAST<br>ESTRUS<br>OR<br>SPERM | DELIV-<br>ERY | DURATION OF<br>PREGNANCY<br>DAYS | DAILY<br>DOSE | TOTAL<br>DOSE | LITTER                  | REMARKS                          |
|-----|-------------------------------|---------------|----------------------------------|---------------|---------------|-------------------------|----------------------------------|
| 33  | 4/27/39                       |               | 11                               | 5             | 55            | 0                       | Bleeding, 5/7/39; aborted        |
| 34  | 4/29/39                       |               | 8                                | 5             | 55            | 0                       | Sperm recovered: no pregnancy    |
| 3   | 9/4/39                        | 9/26/39       | 22                               | 5             | 195           | 5 Alive<br>1 Still-born | Young died                       |
| 5   | 9/1/39                        | 9/23/39       | 22                               | 5             | 180           | 4 Alive                 | Mother and 2 offspring died      |
| 8   | 9/4/39                        | 9/27/39       | 23                               | 5             | 200           | 11 Alive                | 1 offspring survived             |
| 9   | 9/5/39                        |               | 8                                | 5             | 135           | 0                       | Bleeding, 9/12/39; lap. pregnant |
| 11  | 9/1/39                        | 9/23/39       | 22                               | 5             | 180           | 8 Alive                 | Mother and 4 offspring died      |
| 10  | 9/4/39                        | 9/25/39       | 21                               | 1             | 39            | 8 Alive                 | Young died                       |
| 12  | 9/3/39                        | 9/26/39       | 23                               | 1             | 31            | 6 Alive<br>3 Still-born | 2 offspring survived             |
| 17  | 9/5/39                        | 9/27/39       | 22                               | 1             | 39            | 8 Alive                 | 3 offspring survived             |
| 20  | 9/1/39                        | 9/22/39       | 21                               | 1             | 28            | 11 Alive                | Young died                       |
| 3A  | 7/7/39                        | 7/29/39       | 22                               | 1             | 6             | 10 Alive                | Lactation unimpaired             |
| 10A | 7/7/39                        | 7/29/39       | 22                               | 1             | 6             | 7 Alive                 | Lactation unimpaired             |
| 15  | 7/10/39                       |               | 9                                | 1             | 6             | 0                       | Bleeding, 7/19/39; aborted       |

found that abortion occurred in 3 of 14 animals and stillbirths occurred after 2 matings. Lactation was definitely impaired in almost all, and very few of the offspring survived. Two of the mothers died after ingesting 180 mg. of pregneninolone each. In this series, there was no appreciable increase in the duration of pregnancy. On the other hand, Courrier and Jost<sup>6</sup> found that pregneninolone maintained pregnancy in *spayed* rabbits when given combined orally and hypodermically. Although pregneninolone may maintain pregnancy in the spayed rabbit, it showed certain deleterious effects upon the intact pregnant rats in our series. The effect upon lactation is not surprising inasmuch as progesterone, estrogens, and androgens will all inhibit lactation, and pregneninolone exhibits all of these hormonal actions.

Sections of the liver and kidney were examined at the conclusion of the above experiments to determine *toxicity* of the drug, and the findings were tabulated (Table III). Grossly, the liver and kidney of the rats fed pregneninolone differ little from the normal controls except for marked congestion. Histologic section of the liver (Fig. 1) shows the cords markedly swollen and the cytoplasm of the liver cells

TABLE III. ORAL PREGNENINOLONE TOXICITY EXPERIMENT (RATS)

| NO. | KIND                   | DAILY DOSE MG. | TOTAL DOSE MG. | LIVER                        | KIDNEY                       | REMARKS                     |
|-----|------------------------|----------------|----------------|------------------------------|------------------------------|-----------------------------|
| 26  | 2 Mo. male<br>Castrate | 0              | 0              | Cloudy swelling              | Normal                       | Control                     |
| 28  | 2 Mo. male<br>Castrate | 5              | 50             | Normal                       | Cloudy swelling              |                             |
| 29  | 2 Mo. male<br>Castrate | 5              | 50             | Cloudy swelling<br>Hyperemia | Cloudy swelling<br>Hyperemia |                             |
| 30  | 2 Mo. male<br>Castrate | 2.5            | 25             | Cloudy swelling              | Early focal necrosis         |                             |
| 31  | 2 Mo. male<br>Castrate | 2.5            | 25             | Cloudy swelling              | Early focal necrosis         |                             |
| 32  | 2 Mo. male<br>Castrate | 2.5            | 25             | Cloudy swelling<br>Hyperemia | Cloudy swelling              |                             |
| 33  | Mature female<br>Mated | 5              | 55             | Cloudy swelling<br>Hyperemia | Cloudy swelling<br>Hyperemia | Miscarriage                 |
| 34  | Mature female<br>Mated | 5              | 55             | Cloudy swelling              | Cloudy swelling<br>Hyperemia | Miscarriage                 |
| 45  | Mature Anestrus        | 1              | 6              | Cloudy swelling<br>Hyperemia | Cloudy swelling<br>Hyperemia |                             |
| 46  | Mature Pregnant        | 1              | 6              | Cloudy swelling<br>Hyperemia | Early focal necrosis         | Miscarriage                 |
| 3   | Mature Pregnant        | 5              | 195            | Cloudy swelling              | Diffuse necrosis             | 5 normal; 1 stillborn       |
| 5   | Mature Pregnant        | 5              | 180            | Cloudy swelling<br>Hyperemia |                              | 4 normal;<br>mother died    |
| 8   | Mature Pregnant        | 5              | 200            | Cloudy swelling<br>Hyperemia | Focal necrosis               | 11 normal                   |
| 9   | Mature Pregnant        | 5              | 135            | Cloudy swelling<br>Hyperemia | Diffuse necrosis             | Miscarriage<br>after 20 mg. |
| 11  | Mature Pregnant        | 5              | 180            | Cloudy swelling<br>Hyperemia |                              | 8 normal;<br>mother died    |
| 10  | Mature Pregnant        | 1              | 39             | Cloudy swelling<br>Hyperemia | Cloudy swelling              | 8 normal                    |
| 12  | Mature Pregnant        | 1              | 31             | Cloudy swelling<br>Hyperemia | Focal necrosis               | 6 normal; 3 stillborn       |
| 13  | Mature Pregnant        | 1              | 28             | Cloudy swelling<br>Hyperemia | Focal necrosis               | Anestrus                    |
| 17  | Mature Pregnant        | 1              | 39             | Cloudy swelling<br>Hyperemia | Specimen lost                | 8 normal                    |
| 20  | Mature Pregnant        | 1              | 28             | Cloudy swelling<br>Hyperemia | Diffuse necrosis             | 11 normal                   |
| 114 | Mature Pregnant        | 0              | 0              | Cloudy swelling              | Slight cloudy<br>Swelling    | Control                     |

pale and coarsely granular. The individual cell outlines are indistinct. The nuclei in many areas are hyperchromatic but stain distinctly throughout. The sinusoids and central veins are markedly engorged with red blood cells. Thus, cloudy swelling and hyperemia are present in the liver. However, cloudy swelling of the liver was frequently present in the control group and microscopic section differs only in the absence of marked hyperemia, a distinguishing feature in the pregneninolone rats. The kidneys show more significant changes. In 3 of our pregnant animals, a severe diffuse tubular necrosis is present. Four other pregnant rats show an early focal necrosis of the tubules. Two nonpregnant rats show an early focal tubular necrosis also, while the remainder all show a severe cloudy

swelling. A few of our control group showed slight cloudy swelling of the kidney, but never necrosis. The changes in these kidneys are described in detail below.

*Marked Cloudy Swelling; Hyperemia of the Kidney* (Fig. 2).—The cells lining the tubules are markedly swollen and their cytoplasm is pale eosinophilic and coarsely granular; the cell outlines are indistinct. The lumina of the tubules in many areas are almost completely obliterated by the markedly swollen lining cells. Occasionally,

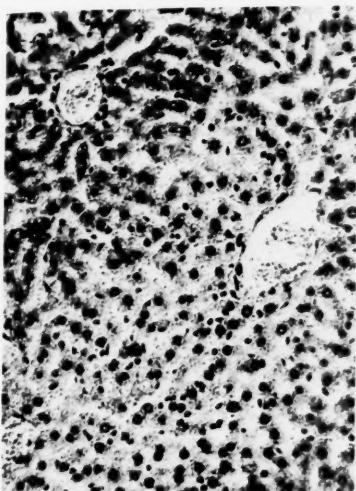


Fig. 1.

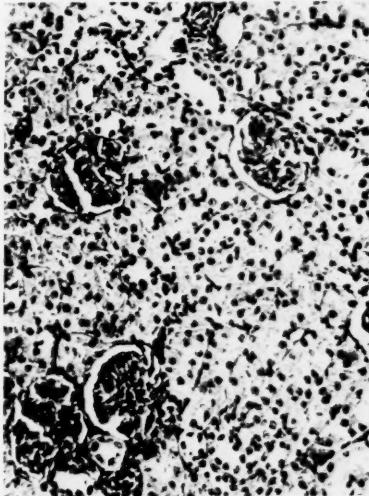


Fig. 2.

Fig. 1.—Liver of Rat 32. After 25 mg. of pregneninolone orally. Note severe cloudy swelling and marked engorgement of central veins and sinusoids. ( $\times 210$ .)

Fig. 2.—Kidney of Rat 45. After 6 mg. of pregneninolone orally. Note severe cloudy swelling. Glomeruli show no changes. ( $\times 190$ .)



Fig. 3.

Fig. 3.—Kidney of Rat 20 after 28 mg. of pregneninolone orally in pregnancy. Severe diffuse necrosis of tubules. Note exudate in glomeruli and hemorrhage in interstitial tissue. ( $\times 170$ .)

Fig. 4.—Kidney of Rat 9 after 135 mg. of pregneninolone orally in pregnancy. Note severe diffuse tubular necrosis and glomerular exudate. ( $\times 180$ .)

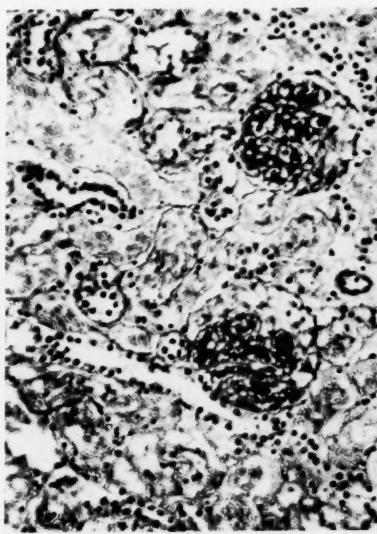


Fig. 4.

the lumina of the tubules contain a pale pinkish structureless material. The capillaries of the glomeruli and of the interstitial tissues are markedly engorged with erythrocytes.

*Focal Necrosis of the Kidney.*—Cloudy swelling as above. Scattered throughout the cortex occasional groups of tubules are found, the architecture of which is indistinct or occasionally almost completely destroyed. These tubules are shadowy in outline and they are filled with a pale eosinophilic amorphous material. The cell outlines cannot be distinguished and the nuclei stain poorly or not at all. The lumina of these tubules contain a fibrillar structureless pink-staining material. Such tubules are found scattered throughout, interspersed with those described above. In these areas are seen occasional extravasations of red blood cells.

*Diffuse Tubular Necrosis* (Figs. 3 and 4).—In many areas, the renal architecture is barely recognizable, only ghostlike, poorly defined outlines of tubules being discernible. The finer histologic details of these tubules are completely obliterated. The lining cells cannot be distinguished, their nuclei do not stain at all and the lumina are filled with a pale eosinophilic structureless debris. The cell outlines cannot be discerned at all. These changes are seen most prominently in the convoluted tubules and the changes are scattered diffusely in sections taken from the renal cortex. Interspersed with these necrotic tubules are occasional small tubules, the architecture of which is in a better state of preservation. Their lining cells are fairly clearly demarcated and the nuclei stain distinctly; however, the cytoplasm is pale, coarsely granular, and the individual cells are swollen, bulging into the lumen, causing almost complete obliteration of the latter. The capillary tufts of the glomeruli in some areas are rather shrunken, and in others hyperemic, and in many of the glomeruli, pale, amorphous eosinophilic material is found within the space between the capillary tuft and Bowman's capsule. The blood vessels of the interstitial tissue are markedly engorged with red blood cells.

No histologic sections were taken on animals found dead in their cages, as we did not wish to confuse our findings with post-mortem changes. In summary, the most characteristic changes were present in the kidneys; tubular necrosis was extensively present in the kidneys of the pregnant rats fed pregnenolone in large amounts.

#### CLINICAL USE OF PREGNENINOLONE

Oral pregnenolone was prescribed for 37 patients complaining of menometrorrhagia, dysmenorrhea, premenstrual tension, amenorrhea and mazoplasia. The drug was administered orally in daily amounts varying from 15 to 30 mg.; the total dosage was limited to 300 mg. during any one month. We endeavored to prescribe it seven to ten days premenstrually which at times was difficult inasmuch as menstrual cycles were extremely variable in the group under study and the drug frequently delayed the following period. Frequently, the treatment was prescribed during an active bleeding phase.

Of the 29 patients with menometrorrhagia, 4 upon further study and laparotomy were found to have definite anatomic changes. Small fibroids were present in 2, bilateral polycystic ovaries in 1, and chronic salpingo-oophoritis in the remaining 1. One patient in whom the small fibroids were present responded temporarily to pregnenolone. Improvement was noted in 12, or 48 per cent, of 25 patients complaining of essential menometrorrhagia. This improvement was temporary unless treatment was continued for several months. A few patients reported diminution in quantity of the flow but complained of increased duration with intermenstrual spotting. The following case reports are of interest:

Miss L. B., aged 23 years, single, menses began at 13 years, regular, 28-day cycles, 3 days' duration, moderate flow, no pain. *Complaint:* Menorrhagia, of two months' duration. The last 2 periods were very profuse, lasting four to seven

days and accompanied by marked weakness. Rectal examination disclosed a normal uterus; the left ovary was tender. The patient was given pregneninolone, 30 mg. daily, beginning on the twenty-sixth day of the cycle. Medication was stopped after three days because the patient complained of nausea and abdominal cramps. The next menstrual period was more profuse and was accompanied by severe dysmenorrhea. Subsequent laparotomy for acute appendicitis revealed polycystic ovaries.

This illustrates the difficulty in differentiating true essential menorrhagia from undiagnosed pathologic changes. This patient's symptoms were aggravated with pregneninolone. It is possible that painless anovulatory bleeding associated with bilateral polycystic ovaries was changed to painful menstruation after the use of oral pregneninolone.

R. G., aged 27 years. *Complaint:* Late puerperal metrorrhagia, six weeks post partum, lasting 10 days. No response to prolan therapy. Pregneninolone, 15 mg. daily was given, with cessation of the flow on the third day. Nausea lasting several hours was noted as a side reaction and vomiting occurred once. There was no recurrence of bleeding.



Fig. 5.



Fig. 6.

Fig. 5.—Persistent proliferative phase before treatment. ( $\times 76$ .)  
Fig. 6.—Late secretory phase after oral pregneninolone. ( $\times 72$ .)

M. L., aged 30 years. Menses: onset at 13 years of age, regular 24-day cycles until five months ago, five to six days' duration, profuse flow. A left oophorectomy (simple cyst) was performed for intractable metrorrhagia of five months' duration; the metrorrhagia continued. Endometrial biopsy revealed an early secretory phase; pelvic pneumogram revealed normal-sized uterus and ovary. Pregneninolone, 30 mg. daily, produced nausea during the first day. Bleeding stopped abruptly but returned. Pregneninolone, 30 mg. daily, produced severe nausea. Irregular bleeding is still present despite a late secretory phase after pregneninolone therapy.

L. J., aged 31 years. *Complaint:* Menorrhagia of four to five months' duration, periods occurring every twenty-one to twenty-four days, five to six days' duration, and of profuse flow. Pregneninolone, 15 mg. daily, for seventeen days, beginning the seventh day of the cycle. The subsequent period was delayed one week, lasted for six days, was profuse in amount but less painful. The dose was repeated the following month; the next period was one week late, scant, and lasted three days. The patient has been followed for one year, and there has been no recurrence of menorrhagia. No side reactions were noted.

G. B., aged 36 years. *Complaint:* Menorrhagia of six months' duration. Periods were regular, with 28-day cycles, four to five days' duration and profuse flow. Endometrial biopsies taken on the fourteenth and seventeenth days of two different cycles showed a proliferating phase. Pregnenolone, 30 mg. daily, was given during the second half of the cycle and produced a delayed period with moderate flow. Endometrial biopsy (premenstrual) showed a late secretory phase. Treatment during two following cycles was also followed by a moderate flow. Recurrence of menorrhagia followed cessation of treatment. No side reactions were reported.

E. H., aged 28 years. *Complaint:* Menorrhagia and dysmenorrhea since onset of menses at age of 15. Periods were regular, every twenty-eight days, lasting fourteen days; they were profuse and accompanied by clots. Biopsy taken on the twenty-fourth day of the cycle revealed polypoid hyperplastic endometrium. After treatment for one week with 30 mg. daily of pregnenolone, biopsy showed a polypoid edematous secretory endometrium with cystic changes (Figs. 5 and 6). Her period began the day biopsy was taken and continued profusely for fifteen days. Headache accompanied ingestion of the drug. Dysmenorrhea as before.

Pregnenolone was of little benefit for the relief of dysmenorrhea in the dosage employed. Of 10 patients treated, only 3 reported improvement, while 2 complained of intensification of pain. One patient, completely relieved by previous testosterone propionate (perandren) therapy, reported only slight improvement with pregnenolone. A small miscellaneous group of patients with premenstrual tension, secondary amenorrhea and mastoplasia showed some temporary benefit (Table IV).

TABLE IV. CLINICAL RESULTS

| NUMBER | COMPLAINT                  | IMPROVED | PERCENTAGE |
|--------|----------------------------|----------|------------|
| 25     | Essential menometrorrhagia | 12       | 48.0       |
| 10     | Dysmenorrhea               | 3        | 30.0       |
| 2      | Premenstrual tension       | 2        |            |
| 1      | Secondary amenorrhea       | 1        |            |
| 1      | Mastoplastia               | 1        |            |
| 37     | —Total number of patients  |          |            |

It is characteristic of patients with functional menometrorrhagia that any endometrial pattern may be found on biopsy. In our series, the usual pattern was an early secretory phase before treatment which changed to a pseudodecidua following therapy. The biopsies of 2 patients complaining of menometrorrhagia showed persistent proliferative endometria; there was transformation in one case (Figs. 5 and 6). These endometrial studies are of little significance in demonstrating progestational activity in the human being during reproductive life. However, in postmenopausal women, Salmon, Walter and Geist<sup>11</sup> were able to produce progestational effects with pregnenolone after priming with estradiol benzoate, and the work of Wenner and Joel<sup>12</sup> confirmed their findings.

Side reactions incident to the use of this drug were frequent but rather mild (Table V). Fifteen patients, or 31 per cent of the total group, complained of nausea, vomiting, abdominal pain, weakness and dizziness, or severe headache. These reactions were more frequently observed when larger doses of pregnenolone (30 mg. daily) were

given, and improved promptly when the dose was reduced. Of 2 patients who could not tolerate this drug, one had a known duodenal ulcer and the other a chronic cholecystitis. However, there were very few instances where the symptoms were severe enough to necessitate withdrawal of the drug. This finding of side effects is at complete variance with the results of all other observers, none of whom reported any disturbing symptoms. In order to determine whether kidney damage resulted from the oral administration of pregnenolone, urinalyses were made at the termination of the various series of treatment; no evidence of kidney damage was found.

TABLE V. UNDESIRABLE SIDE REACTIONS

|                           | DAILY DOSAGE |                     |
|---------------------------|--------------|---------------------|
|                           | 15 MG.       | 30 MG.              |
| Nausea                    | 2            | 1                   |
| Nausea and vomiting       | 3            | 2                   |
| Abdominal pain and nausea | 1            | 4                   |
| Weakness and dizziness    |              | 1                   |
| Severe headache           |              | 1                   |
| Total No. patients: 37    | 6            | 9—Total, 15 (31.0%) |

It had been our original intention to use pregnenolone for the treatment of habitual and threatened abortion, but we hesitated to do so after noting the results of our animal toxicity experiments. The dosage of pregnenolone required to produce necrotizing changes in the kidney in rats is considerable for that animal; even the large and prolonged dose necessary for the treatment of habitual abortion may be well within the margin of safety in the human being. However, the question arose in our minds whether a steroid absorbed through the portal system should not be inactivated by the liver. Is pregnenolone orally active because it destroys the detoxifying function of the liver? Also, would impaired renal activity prevent or delay excretion of the drug, hence augment biologic effects? We would suggest that the patient be carefully watched for possible renal or liver damage should pregnenolone be used for the treatment of habitual or threatened abortion. Although we have obtained no clinical evidence of toxicity and urinalysis has failed to reveal any abnormality to date, no liver or kidney function tests had been performed in our clinical series.

The use of pregnenolone is contraindicated, in our opinion, in known cases of peptic ulcer, cholecystitis, hepatitis, and nephritis. The mild androgenic effects should not be construed as a contraindication, as Greene, Burrill and Ivy<sup>3</sup> have shown that progesterone itself is androgenic in large doses.

#### CONCLUSIONS

Pregnenolone is a potent orally active progestational substance which produces both estrogenic and androgenic effects to a mild degree. It has been found definitely to cause suppression of the gonadotropic function of the anterior pituitary. Definite kidney damage was demon-

strated in rats (chiefly in pregnancy) after administration of this preparation and therefore caution must be exercised in its use in the human being. When given to the intact pregnant rat, it produced abortion and stillbirths, and lactation was definitely impaired. In 31 per cent of our cases, the drug produced mild undesirable side effects, but these untoward reactions were seldom so severe as to necessitate withdrawal of the drug. Pregneninolone proved effective in approximately one-half of our patients complaining of menometrorrhagia but proved to be of little benefit in dysmenorrhea.

We gratefully acknowledge our indebtedness to Dr. Ernst Oppenheimer of the Ciba Corporation who generously supplied us with pregneninolone. We also wish to acknowledge our thanks to Drs. Max Appel and Charles Freed for their invaluable aid.

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#### DISCUSSION

DR. E. S. BURGE.—We have been able to confirm the multiple activities of pregneninolone in the rabbit and white rat. In many other ways our experimental and clinical results were similar to those of Dr. Cohen. I shall discuss only those points at variance.

One must be fully cognizant of the possible toxic properties of any new therapeutic agent. In none of our 51 rats or 19 rabbits, however, was there gross or histologic evidence of damage to the liver, kidneys, or adrenal glands. In an effort to prolong pregnancy in 9 rats, 8 to 120 mg. of pregneninolone was given orally from the eighteenth day of pregnancy until delivery. A tenth pregnant rat, by limiting its water supply to one containing a suspension of crystalline pregneninolone, ingested 655 mg. of the substance, with no ill effects. Using the same method, one of the castrate rats was given 675 mg. in eight days, which together with previous smaller doses, gave a total of 730 mg. in eighteen days. There were no gross or microscopic changes in the organs of any of these animals.

No other writer has reported undesirable clinical side effects after administration of pregneninolone. Hamblen has used up to 2,280 mg. in one fourteen-day period without ill effects. On 21 patients, Dr. Holloway and I have given up to 80 mg. daily, with a highest total dose of 1,140 mg. in fourteen days, with no complaints. One of us, 36 hours ago, took 250 mg. in a single dose, and so far has not been in any distress.

Our clinical results were variable and not always predictable. Unexplained dysmenorrhea was the most promising field, although even in the same patient, alleviation from month to month could not be assured. Unexplained uterine bleeding was not appreciably affected by pregneninolone. In a patient twenty-three years of age who had had only six menstrual periods in her lifetime, her first 2 consecutive periods followed 20 mg. a day of the synthetic preparation for fourteen days, but menses have not returned since pregneninolone was stopped.

All students of uterine physiology believe that one of the corpus luteum's effects is to decrease uterine irritability, and it has been conclusively shown in the rabbit and other animals that the uterus, under a full progesterone effect, does

not react to pituitrin or other oxytocic agents. Most workers believe that the human uterus, *in situ*, responds for all practical purposes similarly to that of the rabbit. Although uterine irritability is but one of a host of factors in the problem of abortion, it seems rather basic, and capable of study in the experimental animal. The following experiments were undertaken:

a. Immature female rabbits were primed over a period of six days with 50 gamma of estrone and then injected with 1 mg. daily of progesterone for five days. At this time, the histologic picture of the uterus was of a full pregestational phase, and grossly the uteri were greatly enlarged and hyperemic. The results were as expected when strips of the uteri were suspended in an optimum bath. There was no response to from 0.01 to 10 units of pituitrin, although, as you can see in the tracings, the spontaneous uterine motility was not affected.

b. Similar rabbits were then "primed" or sensitized as before and no other treatment given for five days. Others were primed and then treated with estrone injections for five days. Both of these groups showed a marked uterine response to even 0.01 unit of pituitrin.

c. Then animals were given nothing but from 1 to 10 mg. daily of pregnenolone. After five days their uteri were in a partial pregestational phase, and you can see the definite response to injections of even small amounts of pituitrin into the bath.

Those animals that were primed and then treated with oral pregnenolone 1 mg. daily for five days, showed a more developed pregestational phase, and a more marked response to pituitrin, while those receiving 5 and 10 mg. daily for five days after priming displayed a complete pregestational effect and the marked response to pituitrin. The increased uterine tone and magnitude of contractions is striking.

In conclusion then, we have a new synthetic preparation which can produce a pregestational endometrium, is estrogenic and weakly androgenic, and increases uterine irritability. Its toxicity I have not been able to demonstrate. Its therapeutic indications are not clear in my mind, and in the face of its effect upon uterine irritability, I do not feel that at present it is indicated in the treatment of threatened abortion.

**DR. EDWARD L. CORNELL.**—A few months ago I was called to see a woman pregnant in her fifth month who in her two previous pregnancies had miscarried and was now having uterine contractions. I had just been informed about this drug, pregnenolone, and I thought it was a good opportunity to try it. I began with a 10 mg. dose and gave her 10 mg. every four hours for the first two days. The contractions stopped. Then she took it every six hours, and finally three times a day. At the end of ten days she was able to discontinue the drug and went along without difficulty for two or three months.

At the beginning of the eighth month she started to have labor pains and by the time I saw her she had produced a 4 cm. dilatation of her cervix. She had begun pregnenolone again, one tablet with the first contraction, and another in a couple of hours. When I saw her six hours later I gave her two tablets and sent her into the hospital. Then I gave her 19 mg. every two hours during the day and night. She was in the hospital for about ten days. The contractions had ceased, but the dilatation remained the same. Then the drug was given every six hours day and night.

She took a total of 4,400 mg. At term she was delivered of a baby weighing 5 pounds and 15 ounces. She has now gone home perfectly well and the baby is all right. There were no hyaline casts or albumin in the urine.

**DR. COHEN (closing).**—Dr. Burge's toxicity experiments were not exactly comparable with ours. He administered the drug orally in huge quantities over a short period of time while I used less of the drug over a longer period—about forty days, which might be regarded as equivalent to eighteen months in the human being. It is possible that a long period of administration of pregnenolone may affect the kidney whereas a large dose over a shorter period may have no effect.

I cannot account for the lack of nausea in patients treated by Dr. Burge. It is surprising to us that Dr. Burge reported his best results in cases of dysmenorrhea,

since we had our poorest results in this condition. One of our patients who was treated for menorrhagia without pain was given pregneninolone and subsequently complained of violent dysmenorrhea. Shortly thereafter, she was laparotomized and found to have polycystic ovaries. It is possible that her painless anovulatory bleeding was changed to painful menstruation by means of this progestin-like preparation.

We have not had the courage to use this drug in complications of pregnancy because of our animal experiments. Perhaps if Dr. Cornell continued the drug during the puerperium, he would also have suppressed lactation in his patient.

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## Society Transactions

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### CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF MAY 17, 1940*

The following papers were presented:

**An Evaluation of Androgenic Therapy in Gynecologic Practice.** Dr. John W. Huffman. (For original article, see page 674.)

**Laboratory and Clinical Experience With Oral Pregneninolone.** Drs. Melvin R. Cohen, and Irving F. Stein. (For original article, see page 713.)

**Presentation of a Specimen of Malignant Mixed Tumor of Uterus.** Dr. Herman A. Strauss.

**Ovarian Ectopic Pregnancy.** Dr. Alfred F. Kobak.

**The Rate of Entrance of Amniotic Fluid Into the Pulmonary Alveoli During Fetal Respiration.** Dr. Franklin F. Snyder (by invitation).

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

*(Appears in January, April, July, October)*

**American Gynecological Society.** *President*, E. J. Litzenberg. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June, 1941, Colorado Springs, Colo.

**American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, Frederick H. Falls, Chicago, Ill. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.

**Central Association of Obstetricians and Gynecologists.** *President*, Jennings C. Litzenberg, Minneapolis, Minn. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.

**South Atlantic Association of Obstetricians and Gynecologists.** *President*, M. P. Rucker, Richmond, Va. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.

**A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Norman F. Miller, Ann Arbor, Mich. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June 2 to 6, 1941, Cleveland, Ohio.

**New York Obstetrical Society.** *President*, Thomas C. Peightal. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

**Obstetrical Society of Philadelphia.** *President*, Roy W. Mohler. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

**Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

**Brooklyn Gynecological Society.** *President*, Frances Doyle. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

**Baltimore Obstetrical and Gynecological Society.** *President*, N. J. Eastman. *Secretary*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

**Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

**Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

**Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

**Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, April, and June.

**Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

**New England Obstetrical and Gynecological Society.** *President*, Thomas Almy. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.

**Pacific Coast Obstetrical and Gynecological Society.** *President*, Alice F. Maxwell. *President-Elect*, John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. Next meeting, San Francisco, Calif., Nov. 6 to 9, 1940.

**Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K Street, N. W., Washington, D. C. Fourth Saturday, October to May.

**New Orleans Obstetrical and Gynecological Society.** *President*, H. C. McGee. *Secretary*, H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.

**St. Louis Gynecological Society.** *President*, Percy H. Swahlen. *Secretary*, Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.

**San Francisco Gynecological Society.** *President*, T. Floyd Bell. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

**Texas Association of Obstetricians and Gynecologists.** *President*, H. Reid Robinson, Galveston, Texas. *Secretary-Treasurer*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Marlin, Texas, October, 1940.

**Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Russell W. Allen. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

**Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.